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REVIEW

Harnessing Nanocarriers to Improve Psychiatric Treatment: Progress, Limitations, and Future Directions

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Abstract: To address clinical bottlenecks of traditional antipsychotic drugs, including delayed onset of action, significant peripheral side effects, and poor patient compliance, nanodelivery systems offer a feasible approach through their unique physicochemical properties to improve drug solubility, optimize in vivo transport, and enhance blood-brain barrier (BBB) penetration efficiency. This review focuses on the application potential and translational value of nanodelivery systems in psychiatric disorders. We systematically summarize recent advances in the construction strategies of mainstream nanocarriers, including lipid-based, polymer-based, inorganic nanomaterials, Metal-Organic Frameworks (MOFs), and Extracellular Vesicles (EVs), as well as commonly used nanoparticle preparation and characterization techniques. We briefly discuss key challenges facing nanoformulations, such as long-term safety, large-scale production, and batch-to-batch consistency, and highlight future directions driven by artificial intelligence and precision medicine. This review aims to provide insights for the rational design of nanodelivery systems for psychiatric disorders and to advance the development of precision psychiatry.

Keywords: antipsychotics, psychiatric disorders, BBB, nanoformulations, drug delivery, lipid-based nanoparticles, polymer-based nanoparticles, inorganic nanomaterials, MOFs, EVs

Introduce

Introduction to Psychiatric Disorders

Schizophrenia, depression, bipolar disorder and other psychiatric conditions are major contributors to the global disease burden and account for a substantial proportion of global years lived with disability.[1] Psychiatric disorders stem from the complex interaction of psychological stress sources, social environment and physiological foundations (such as genetic susceptibility and abnormal brain structure).[2,3] Notably, functional dysregulation in neural circuits involving the limbic system, prefrontal cortex, and hippocampus is closely linked to the pathophysiology of psychiatric conditions. The brain relies on neurotransmitters—specifically serotonin, dopamine, and gamma-aminobutyric acid (GABA)—to facilitate interneuronal communication through physiological signaling cascades. Dysregulation in the synthesis, release, or reuptake of these neurotransmitters can severely compromise critical biological processes, including sleep-wake rhythmicity, and mood modulation, which in turn promotes the initiation and progression of psychiatric conditions.[4] Presently, the most extensively studied neurotransmitters in psychiatric research include monoamines, such as dopamine and the aforementioned serotonin, amino acid neurotransmitters like glutamate, and other mediators including acetylcholine, melatonin, and histamine. Targeted neurotransmitter imbalance is the core treatment strategy of a variety of psychiatric disorders, which can be enhanced by nanocarrier-mediated drug delivery. Significantly, the regulation of serotonin (5-HT) and dopamine receptors is a common pharmacological method for alleviating the symptoms of

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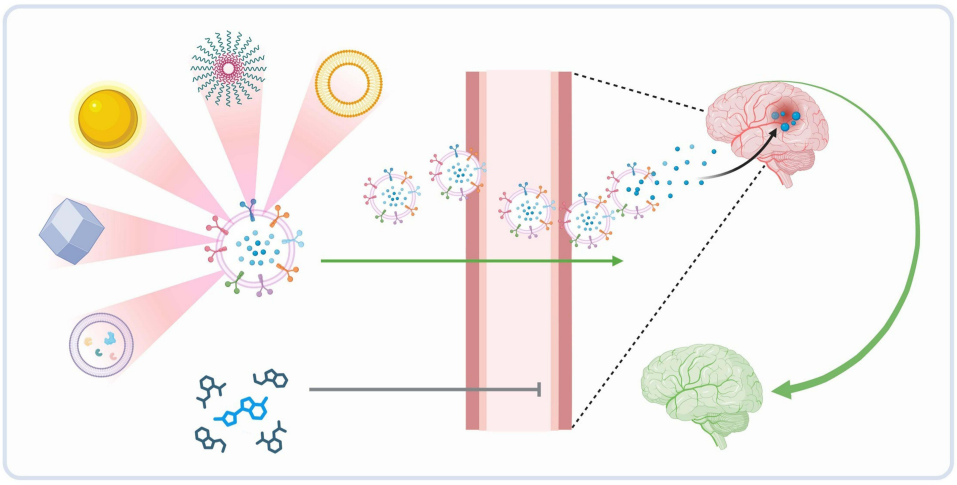
Graphical Abstract



schizophrenia, and nanocarriers may improve the specificity and effectiveness of such receptor-targeting drugs. For example, first-generation antipsychotic drugs (eg, haloperidol and chlorpromazine) mainly exert a high-affinity antagonistic effect on dopamine D2 receptors and effectively control positive symptoms, accompanied by a higher incidence of extrapyramidal side effects.[5] Second-generation antipsychotics are characterized by rapid dissociation from the dopamine D2 receptor and high-affinity antagonism of the serotonin 5-HT2A receptor. These properties are associated with a lower risk of extrapyramidal side effects and may help improve negative and cognitive symptoms.[6] Upregulating the levels of monoamine neurotransmitters and enhancing their function is the core mechanism of antidepressants.[7] We have summarized representative psychiatric disorders, their relevant brain regions, and key neurotransmitters in Table 1. It should be noted that ongoing research encompasses a broader range of conditions and mechanisms beyond those listed. In addition to explaining issues with neurotransmitters, research shows strong immunity-psychiatric disorders correlation. Upon differentiation into the pro-inflammatory M1 phenotype, microglia

Table 1 Common Psychiatric Disorders and Their Associated Brain Regions and Neurotransmitters

Disease	Symptom	Key Pathological Regions	Related Neurotransmitters	Ref
Depression	Be down in spirits, sense of guilt, suicide ideation, changes in attention, appetite and sleep, etc	Ventral tegmental area-nucleus accumbens-medial prefrontal cortex (VTA-NAc-mPFC) neural circuit; The hypothalamic- pituitary-adrenal (HPA) axis	Dopaminergic, serotonergic, GABA-ergic and glutamatergic systems	[11–14]
Anxiety disorder	Excessive fear and worry, have nightmares, palpitations, difficulty breathing, etc	Prefrontal cortex-amygdala circuits; Cortical-striatal-limbic circuit	5-HT system, Glutamate, GABA	[15–18]
Schizophrenia	Positive symptoms (eg, hallucinations/delusions); Negative symptoms (eg, poverty of speech and thought)	Mesolimbic circuit and Mesocortical circuit	Dopaminergic system, Glutamate, GABA	[19,20]
Bipolar disorder	Bipolar I disorder characterized by syndromal manic episodes; Bipolar II disorder involving syndromal hypomanic episodes plus major depressive episodes	Prefrontal-limbic-subcortical network	Dopamine, glutamate	[21–25]
Obsessive–compulsive disorder	Obsessive behaviors such as hoarding disorder, scrupulosity, obsessional jealousy	Cortico-striato-thalamo-cortical (CSTC) circuit	Serotonin, dopamine and glutamate	[26–28]
Posttraumatic Stress Disorder	Revisiting painful memories, nightmares, flashbacks, and startle reactions, etc	Amygdala and ventromedial prefrontal cortex; HPA axis	5-HT system, Dopaminergic system, glutamate, GABA	[29–32]

release pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), a process closely linked to the onset of neuronal dysfunction and psychiatric disorders.[8,9] Despite the complexity of the pathophysiology of psychiatric disorders, most existing studies focus on cerebral areas that control perception, behavior, emotions, and other facets of life because psychiatric disorders are closely linked to changes in specific brain regions' function and structure.[10] Further intensive research on the brain will continue to be beneficial for drug treatment of psychiatric disorders.

Long-Standing Challenges and Current Limitations of Drug Treatment for Psychiatric Disorders

Pharmacotherapies remain a fundamental and indispensable component of clinical treatment for psychiatric disorders.[33] The WHO's list of essential medicines for psychiatric disorders serves as a valuable reference for countries when formulating their own national essential medicines lists.[34] Psychiatric disorders are similar to chronic diseases and require long-term medication to prevent reoccurring symptoms. In addition, symptoms can be managed by medication injections during severe psychiatric disorder episodes. While pharmacotherapy for psychiatric disorders has advanced considerably in clinical practice, current treatments still face a dual dilemma: persistent hurdles such as central nervous system (CNS) physiological barriers, first-pass metabolism, and mucociliary clearance, together with inherent limitations including rapid systemic elimination, adverse reactions, and delayed onset. These issues collectively reduce patient compliance and limit optimal therapeutic efficacy.[35]

Physiological Barriers

BBB

The BBB, consisting of tightly connected cerebral endothelial cells, astrocytes, pericytes, and the basement membrane, serves as a critical physiological barrier for pharmaceutical delivery in psychiatric disorder therapies.[36] It selectively mediates nutrient translocation, inhibits pathogen infiltration, and serves a pivotal role in sustaining brain homeostasis by tightly governing the exchange of substances between the bloodstream and the cerebral parenchyma. The intact BBB enables the permeation of lipophilic small molecules with molecular weights under 500 Da, while excluding roughly 98% of small-molecule compounds and all large-molecule drugs.[37,38] Although they can cross the BBB, several antipsychotic agents—including amisulpride, paliperidone, risperidone (RSP), aripiprazole, and olanzapine—have been identified as substrates of the P-glycoprotein (P-gp) efflux pump, which actively extrudes them from the brain parenchyma.[39] These physiological barriers constitute long-standing challenges in psychiatric drug delivery, and insufficient drug accumulation in the brain remains a major obstacle to achieving therapeutic efficacy. Therefore, augmenting cerebral drug concentrations is fundamental to effectively treating psychiatric and neurological disorders.

Blood-Cerebrospinal Fluid Barrier (BCSFB)

BCSFB consists of choroid plexus epithelial cells and the tight junctions between them. This barrier maintains CNS homeostasis by selectively regulating the exchange of substances between the blood and the cerebrospinal fluid, while also further intercepting drugs (eg, via mechanisms such as P-gp efflux pumps) from entering the cerebrospinal fluid.[40,41] Drug therapy still faces challenges in penetrating target cells within the brain. Notably, brain parenchymal penetration represents an often-overlooked yet critical barrier for CNS drug entry.[42] A major limitation of current therapies is the lack of delivery systems capable of crossing multiple central barriers simultaneously. Even when drugs successfully penetrate the BBB, they are frequently impeded by the BCSFB, resulting in uneven distribution in target regions and suboptimal therapeutic efficacy.

Metabolism and Multiple Efflux Protein Barriers

Metabolic barriers and drug clearance mediated by efflux proteins constitute two persistent obstacles. Systemically, the hepatic first-pass effect markedly reduces the bioavailability of oral drugs.[43] Within the CNS, drugs crossing the BBB are further degraded by cerebral cytochrome P450 enzymes, while P-gp and other multidrug efflux pumps actively expel them from the brain parenchyma.[44] Together, these mechanisms hinder the maintenance of effective drug concentrations at target sites.

Inherent Deficiencies and Limitations of Administration Routes

Different administration routes present long-standing practical challenges and inherent technological limitations, as detailed below:

Oral Administration

Oral drug delivery continues to be the predominant administration route in clinical psychiatric practice, attributed to its convenience, favorable patient adherence, and non-intrusive characteristics. Nevertheless, in the context of therapeutics engineered for CNS targeting, oral administration often gives rise to hurdles linked to suboptimal pharmacokinetic behaviors and insufficient brain bioavailability.[45] A key underlying reason lies in the physicochemical features of most antipsychotic agents are generally highly lipophilic and exhibit low aqueous solubility, which characteristic results in restricted dissolution within the gastrointestinal lumen and compromised absorption efficiency across the intestinal epithelial barrier. Many antipsychotics undergo Phase I drug metabolism in the intestinal mucosa and liver, where they are metabolized by Cytochrome P450 enzymes, such as CYP2D6, CYP1A2, and CYP3A4, which results in lower active concentrations before they reach systemic circulation.[46,47] Notably, the hepatic first-pass impact significantly affects the metabolism of clozapine, an atypical antipsychotic that is therapeutically recommended for refractory schizophrenia, resulting in an oral bioavailability of less than 27%.[48] These pharmacokinetic hurdles also represent common challenges across the field, which directly impair therapeutic efficacy and increase interindividual pharmacokinetic variability.

Nose-to-Brain Delivery

To bypass gastrointestinal degradation and hepatic metabolism, intranasal delivery has gained attention as a promising non-invasive strategy for direct nose-to-brain transport. This route exploits the unique anatomical and physiological connections between the nasal cavity and the CNS, particularly via the olfactory epithelium and trigeminal nerve pathways, enabling rapid and targeted drug delivery while avoiding systemic metabolic clearance.[49] Nevertheless, formulation challenges remain, including limited dosing volume, rapid mucociliary clearance, and the risk of nasal mucosal irritation, all of which necessitate careful optimization of drug formulation and delivery devices.[50] Overcoming these limitations requires a new formula to enhance mucosal adhesion/tolerance and a special delivery system that can penetrate deep and reliable nasal deposition.

Transdermal Drug Delivery

As a long-term adjunctive therapeutic route, transdermal drug delivery aims to address poor oral compliance and the pain associated with injections. However, a persistent key obstacle is the strong barrier function of the stratum corneum, which impedes drug absorption and diffusion.[51] The quetiapine transdermal patch reported by Agrawal et al achieved a cumulative release rate of 82.98% over 20 hours, with bioavailability superior to conventional formulations.[52] However, this formulation lacks a brain-targeting design, indicating that there is still significant room for optimization in the brain-targeting capabilities of current transdermal formulations.

Intravenous/Intramuscular Administration

Intravenous and intramuscular administration are widely used as emergency treatments to rapidly control symptoms during acute episodes of severe psychiatric disorders.[53] However, intravenous administration shows poor brain targeting because it cannot cross the multiple physiological barriers of the CNS. Conventional injectable formulations act quickly but have a short duration of action and require frequent dosing, leading to low patient compliance. Although novel formulations such as RSP in situ microspheres have achieved initial technical progress toward rapid onset and long-acting effects via biphasic release, these clinically available preparations still need further optimization.[54] Thus, injectable formulations that combine rapid onset with sustained release remain scarce in clinical practice, making it difficult to meet the integrated clinical demand for both acute symptom control and long-term maintenance therapy in severe psychiatric disorders.

Adverse Reactions and Compliance

Antipsychotic medications are often linked to dose-related and individual-specific adverse effects, which can markedly undermine patients' treatment adherence and overall clinical outcomes. The metabolic disruptions, such as significant weight gain connected with olanzapine and chlorpromazine, carry long-term health risks. Additionally, hyperprolactinemia usually occurs with drugs such as RSP and paliperidone, while drugs such as aripiprazole and chlorpromazine are more likely to cause sedation. QT interval prolongation is a serious heart risk that can be caused by certain antipsychotic drugs, including zilaxidone and esicilopran. Extrapyramidal symptoms, meanwhile, remain a defining feature of typical antipsychotics, most notably haloperidol.[55] Epidemiological data show that drug adherence to psychiatric patients is a common problem, affecting 50% to 75% of individuals. Intolerance to side effects is the main reason, accounting for about 71.4% of the termination of treatment.[56] What's more, many psychiatric medications have a delayed therapeutic effect that is a factor further worsens adherence issues. For example, conventional antidepressants often require several weeks to exert their full therapeutic effect, and the rate of inadequate response to first-line treatment is nearly 30%.[57,58] Beyond that, some antipsychotic drugs require frequent injections, which can cause physical discomfort and psychological distress, further reducing patient adherence.

We summarize the aforementioned remaining challenges and current limitations associated with pharmacotherapy for psychiatric disorders in Table 2. Given these multiple clinical bottlenecks, there is an urgent need to develop novel delivery strategies to break through the existing therapeutic paradigm. Therefore, the construction of rationally designed and targeted nano-drug delivery systems provides a promising strategy to overcome these obstacles.

Advantages of Nano Delivery System

Overcoming the BBB is still a major hurdle to neurological and psychiatric disorders. Contemporary advances in nanotechnology offer a viable approach for efficiently delivering therapeutic molecules to the brain through engineering nanoparticles (NPs).[42] The success of these NPs depends largely on two core design characteristics: their size and surface chemical properties. Studies show that the penetration of NPs into the BBB in the diameter range of 50–100 nm is optimally balanced, because the permeability usually decreases with the increase of size.[59–61] Receptor-mediated transcytosis (RMT) represents a promising strategy for brain targeting. It enables efficient BBB penetration via endogenous receptors such as the transferrin receptor (TfR), with high specificity and clinical translational potential.[62] In addition to RMT, other endogenous pathways offer alternative routes for BBB crossing. Carrier-mediated transport (CMT) relies on nutrient transporters including GLUT1 to facilitate brain uptake.[63] Cell-mediated delivery (eg, using macrophages) shows unique advantages for psychiatric disorders due to its excellent biocompatibility and intrinsic BBB-penetrating ability.[64] In nanodelivery research for psychiatric disorders, RMT is widely applied, whereas CMT and cell-

Table 2 Examples of Long-Standing Challenges and Current Limitations in Pharmacotherapy for Psychiatric Disorders

Category	Subcategory	Long-Standing Challenge	Current Limitation
Physiological barriers	BBB	Tight junctions, P-gp and other efflux pumps	Excludes most small-molecule drugs and all macromolecular drugs
	BCSFB	Tight junctions, P-gp and other efflux pumps	Secondary drug interception
	Metabolic/efflux barrier	First-pass metabolism; Cerebral CYP450 enzymes; P-gp and other efflux pumps	Drug inactivation and efflux before/after brain entry
Administration route	Oral administration	Poor solubility; Incomplete GI dissolution; Hepatic first-pass metabolism	Unavoidable first-pass effect; Poor brain-targeted accumulation
	Nose-to-brain delivery	Mucociliary clearance; Nasal mucosal irritation	Unstable brain delivery efficiency
	Transdermal drug delivery	Stratum corneum barrier	Lack of brain-targeted design strategies
	Intravenous/Intramuscular Administration	Poor brain targeting, requires frequent dosing	Low patient compliance
Adverse effects and compliance	Adverse reactions	Weight gain, extrapyramidal symptoms, etc	Difficulty balancing efficacy and safety; Limited adverse event management tools
	Patient compliance	Poor adherence; Adverse reaction intolerance as a major cause of discontinuation	Delayed therapeutic onset; Inconvenient routes; Lack long-term adherence strategies

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mediated strategies remain at the exploratory stage. Nevertheless, studies have demonstrated that mannose-modified NPs can achieve brain accumulation by targeting GLUT1.[65] Macrophage-based delivery systems have also shown significant anti-inflammatory and antidepressant effects in inflammation-related depression models.[66]

Table 3 shows representative nanodelivery systems based on endogenous transport pathways, including RMT, CMT and cell-mediated delivery. Notably, these pathways are not the only routes for crossing the BBB. Adsorptive-mediated transcytosis, the nose-to-brain pathway, and other approaches also enable effective brain delivery.[67]

Nanocarriers offer value that goes far beyond their now well-established targeting abilities. Reformulation of drugs with poor physicochemical properties is one of their key benefits. For example, encapsulating hydrophobic antipsychotics within polymeric micelles with low critical micelle concentrations stabilizes the drugs in the gastrointestinal tract, a strategy that notably boosts oral bioavailability.[74] What's more, NPs open up innovative administration routes that get around traditional barriers. Intranasal nanoparticle formulations leverage olfactory and trigeminal neural pathways to bypass systemic metabolism, achieving direct drug delivery to CNS. Lithium-loaded nanohydrogel has successfully put this idea into practice, providing a fast and non-invasive way to target the brain.[75] Nasal nanocomposite hydrogels encapsulating antipsychotic drugs have shown prolonged brain retention and sustained therapeutic effects in treating schizophrenia.[76] Long-acting injectable formulations, including paliperidone palmitate and emerging RSP-based copolymer depots, can maintain stable plasma drug concentrations over extended intervals, improving patient adherence and treatment consistency.[77,78] RSP can be delivered minimally invasively and sustainedly via sophisticated delivery systems

Table 3 Representative Nanodelivery Systems for Psychiatric Disorders Based on Endogenous Transport Pathways (Including RMT, CMT and Cell-mediated Delivery)

Targeted Receptors	Targeting Ligand	Nanoparticle	Durg	Disease	Transport Mechanism	Comments (Key Outcomes & Significance)	Ref
GLUT1	Mannose	Mannose-PEG600-lipoic acid (Man-LA)	H_2S donor	Autism spectrum disorder (ASD)	CMT	• Identified Aldh3b1 as ASD aerobic glycolysis target • Dual precise ASD therapy by Man-LA targeted delivery	[65]
Central M1-type microglia cells	CTLA-4	CTLA-4-modified live macrophages (CAR-M-UZPM)	Melatonin	Inflammation-related depression	Cell-mediated delivery	• Efficiently penetrates BBB • Inhibits microglial M1 polarization • Exerts vaccine-like anti-inflammatory and antidepressant effects	[66]
TfR	Transferrin	Chitosan NPs (Tf-NP)	Ziprasidone	Schizophrenia	RMT	• Direct nose-to-brain transport >92% • Brain/plasma ratio = 1.50 (vs 0.13 for IV injection, 1.31 for unmodified NPs)	[68]
	Transferrin	Alginate nanogels (BT-ROS-GA-PA ANs)	Glycyrrhizic acid (GA) and Paeoniflorin (PA)	Major depressive disorders	RMT	• 2- to 3-fold increase in BBB transport • Elevated drug levels in hippocampus	[69]
	D-T7 peptide	Dual-targeted NPs (Asp@TMNPs)	Aspirin	ASD	RMT	• 3.39-fold higher BBB transcytosis • Alleviates neuroinflammation and rescues ASD phenotypes	[70]
LRP1	KS-487 peptide	Targeted micelles	KS-133	Schizophrenia	RMT	• Brain peak concentration ~70 nM > IC_{50} (25 nM) • Uniform distribution across core brain regions	[71]
Acetylcholine receptor	RVG	RVG-modified exosomes (RVG-BDNF-Exos)	Brain-derived neurotrophic factor (BDNF)	Depression	RMT	• Enriched in hippocampus and prefrontal cortex • Significantly increased BDNF protein levels	[72]
Albumin receptor	Human serum albumin (HSA)	Quetiapine-HSA NPs (QP-NP)	Quetiapine	Schizophrenia	RMT	• 4.9-fold higher brain targeting vs oral solution	[73]

as poly(lactic-co-glycolic acid) (PLGA) -based microneedle patches, which promote self-administration while reducing the frequency of doses.[79]

By integrating physicochemical tuning, receptor-mediated transport, and controlled release kinetics, these systems address core pharmacokinetic challenges, enhancing brain targeting while limiting off-target effects. While promising, challenges including nanocarrier biocompatibility, immunogenicity, large-scale manufacturing, and precise targeting specificity remain critical areas for future research to fully realize their clinical potential in psychiatric disorder management.

Common Carrier Materials for Nanoparticle Delivery Systems

Advantages of Nanocarrier-Mediated Delivery

Nanocarriers critically orchestrate the pharmacokinetic fate and brain-targeting precision of therapeutics, with their physicochemical composition fundamentally determining biodistribution and cellular interactions. Lipid NPs facilitate intestinal lymphatic transport, enabling labile drugs to bypass enzymatic degradation and hepatic first-pass metabolism—key barriers that frequently compromise oral bioavailability.[80] In clinical practice, lipid NPs effectively enhance BBB permeability through lipid-mediated membrane fusion, showing good potential as a brain-targeted drug delivery system.[81]

At the same time, polymer nanocarriers have the advantage of highly modular design. By introducing stimulation response connection units such as pH-sensitive amide bonds and redox unstable disulfide bonds, such carriers can achieve time-time controllable payload release in the acidic or reducing microenvironment unique to pathological brain areas.[82,83] In addition, its surface charge can be dynamically reversed with the protonation state, further promoting the engulf process of cells.[84]

Inorganic NPs now go beyond standard drug delivery for psychiatric disorders. Iron-based magnetic NPs can serve to achieve MRI-guided precise drug delivery and upregulation of the chemokine receptor CXCR4. This receptor enhancement promotes the homing of endogenous stem cells to sites of neural injury, providing additional therapeutic support.[85] Black phosphorus (BP) nanosheets achieve another form of synergy by combining photothermal-mediated BBB modulation with reactive oxygen species (ROS) scavenging. This combination is capable of both neuroprotective effects and reversibly enhancing BBB permeability, which is a dual mechanism that is hard to achieve with traditional carriers.[86,87]

Collectively, through rational design, nanocarriers achieve robust physicochemical stability and stimuli-responsive release behavior. These properties work together to avoid premature clearance, minimize off-target toxicity, and facilitate cellular uptake.[88,89]

Preparation Methods of Nanocarriers

The preparation method of a nanodelivery system directly affects its physicochemical properties, which in turn determine its in vivo behavior and therapeutic efficacy.[90] Based on the type of carrier, the commonly used preparation methods and their advantages and limitations are summarized in Table 4.

Evaluation Methods for Nanocarriers

Evaluating the critical quality attributes of nanocarriers requires a thorough characterization approach to ensure their suitability for delivering therapeutic agents against psychiatric disorders. Generally, the evaluation should be performed from three aspects: physicochemical properties, drug-loading performance, as well as biological function and safety.[99]

Physicochemical characterization serves as the essential foundation for quality control of NPs. When particle size and distribution are measured by dynamic light scattering (DLS), the polydispersity index (PDI) should be less than 0.3 to indicate uniform particle size.[100] In addition, an absolute zeta potential value higher than 30 mV reflects good colloidal stability, which is beneficial for long-term stability.[101] Characterization of nanoparticle morphology and structure relies on transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM).[102] X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) are usually employed for determining crystalline structure and chemical composition.[103]

Table 4 Preparation Methods, Advantages, and Disadvantages of Common Nanocarriers

Carrier Type	Preparation Methods	Advantages	Disadvantages	Ref
Lipid-based NPs	• Microfluidic Process; • Single/Double; • Emulsification; • Thin Film Hydration; • Nanoprecipitation; • Nonsolvent Emulsification	• Microfluidics: narrow PDI, high reproducibility; • Emulsification: high encapsulation efficiency; • Thin-film hydration: uniform size, mature process; • Nanoprecipitation: simple, easy parameter control; • Nonsolvent emulsification: organic solvent-free, mild	• Microfluidics: high equipment cost; • Emulsification: organic solvent removal required; • Thin-film hydration: poor batch-to-batch reproducibility; • Nanoprecipitation: limited drug loading; • Nonsolvent emulsification: difficult size control	[91]
Polymer-based NPs	• Emulsion Techniques; • Nanoprecipitation; • Dialysis; • Ionic gelation; • Spray drying	• Emulsification: scalable; • Nanoprecipitation: simple, pH-responsive preparation; • Dialysis: easy to operate; • Ionic gelation: low cost; • Spray drying: scalable, good reproducibility	• Emulsification: residual organic solvents; • Nanoprecipitation: poor drug stability; • Dialysis: time-consuming, hard to scale up; • Ionic gelation: difficult size control; • Spray drying: large particle size	[92]
Inorganic NPs	• Chemical reduction; • Co-precipitation; • Thermal decomposition; • Hummers' method	• Chemical reduction: controllable particle size; • Co-precipitation: simple, scalable; • Thermal decomposition: uniform particle size, high crystallinity; • Hummers' method: high oxidation degree, mature process	• Chemical reduction: residual solvent issues; • Co-precipitation: broad particle size distribution, easy agglomeration; • Thermal decomposition: high temperature requirement, high cost; • Hummers' method: strong acid involved, long reaction time	[93–95]
MOFs	• Solvothermal/Hydrothermal; • Solvent-free synthesis; • Microwave-assisted synthesis; • Electrochemical synthesis; • Co-precipitation method	• Solvothermal/Hydrothermal: high crystallinity, wide applicability; • Solvent-free synthesis: eco-friendly, scalable; • Microwave-assisted synthesis: high yield, fast; • Electrochemical synthesis: mild conditions, low energy consumption; • Co-precipitation: simple, high yield	• Solvothermal/Hydrothermal: high temperature/pressure, high energy consumption; • Solvent-free synthesis: typically low crystallinity; • Microwave-assisted synthesis: high equipment cost; • Electrochemical synthesis: requires specialized equipment; • Co-precipitation: limited morphology control	[96,97]
EVs	• Ultracentrifugation; • Size-Exclusion Chromatograph; • Immunomagnetic Bead Method	• Ultracentrifugation: high purity, wide applicability; • Size-Exclusion Chromatography: good EV integrity, high purity; • Immunomagnetic Bead Method: high specificity	• Ultracentrifugation: high equipment cost, demanding technical requirements; • Size-Exclusion Chromatography: time-consuming, sensitive to parameters; • Immunomagnetic Bead Method: high cost	[98]

Drug loading characterization includes the evaluation of drug loading content, encapsulation efficiency, and in vitro drug release behavior. Drug loading content and encapsulation efficiency are routinely determined by high-performance liquid chromatography (HPLC), which reflects the drug-carrying capacity of NPs. In vitro release profiles are investigated under simulated physiological and pathological microenvironments (eg, acidic pH, high glutathione concentration) to evaluate the sustained-release property and stimuli-responsive drug release ability of the delivery system.

For biological function and safety assessment in the context of brain targeting for psychiatric disorders, cellular uptake, BBB penetration (using the Transwell model), and pharmacokinetic parameters (eg, in vivo biodistribution and brain accumulation) should be examined. In addition, cytotoxicity, hemolysis rate, and relevant animal models must also be evaluated to ensure in vivo safety.[104]

This paper systematically reviews strategies for delivering antipsychotic drugs using various nanocarrier platforms, including lipids (Figure 1A), polymers (Figure 1B), inorganic nanomaterials (Figure 1C), MOFs (Figure 1D), and EVs (Figure 1E). Our analysis aims to provide a conceptual foundation for the rational design of nanocarriers that overcome the multifaceted challenges of delivering drugs for psychiatric disorders.

Nanomaterials for Antipsychotic Treatment

Based on the basic characteristics of nanocarriers explained in Chapter 2, this section further elaborates on the practical applications of various nanomaterials in the delivery of psychotropic drugs, highlighting their unique value and potential in solving the bottleneck of drug treatment for psychiatric disorders.

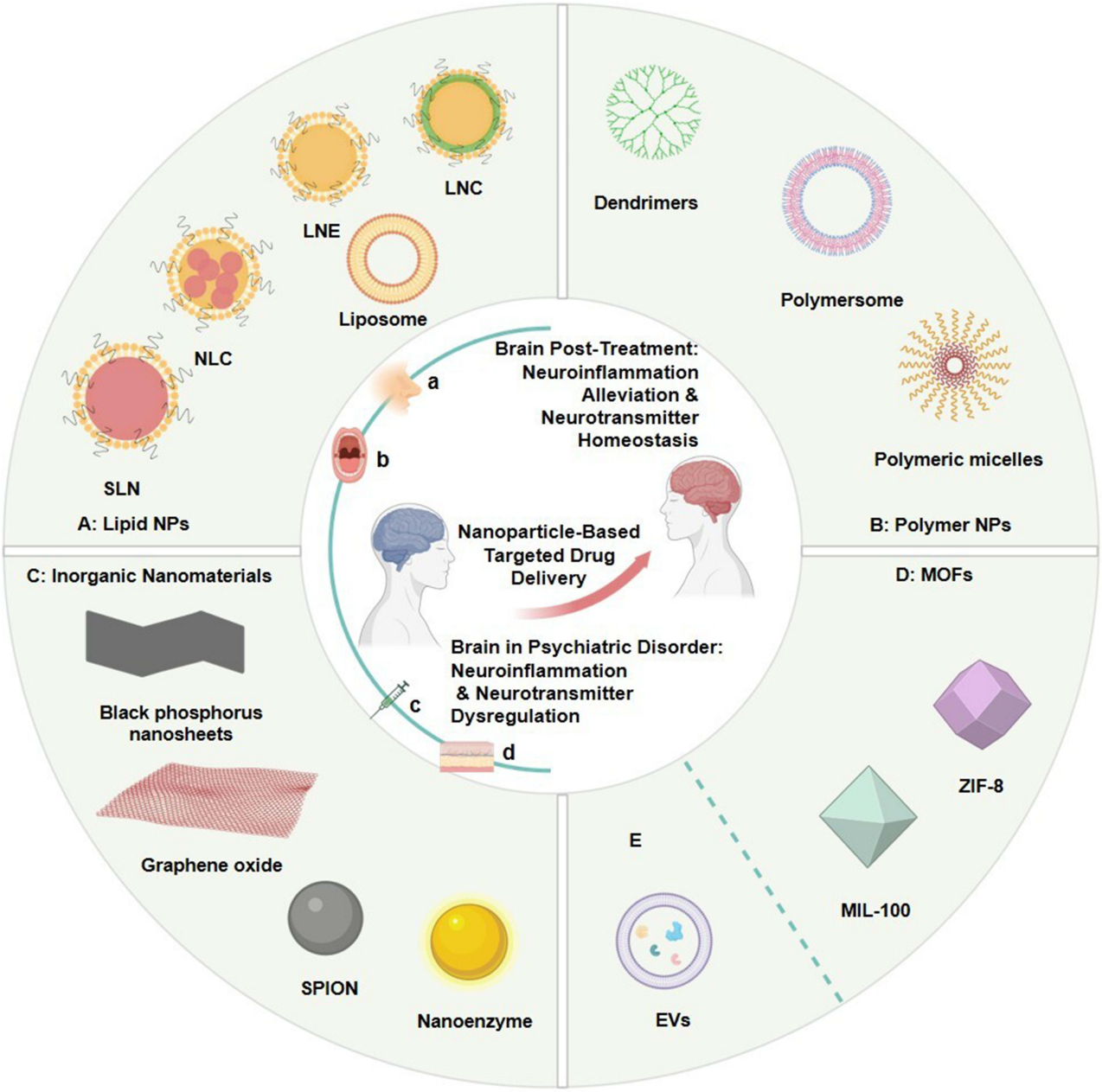

Figure 1 Nanoformulations for delivering drugs for psychiatric disorders ((**A**) Lipid NPs; (**B**) Polymer NPs; (**C**) Inorganic Nanomaterials; (**D**) MOFs; (**E**) EVs) and their administration routes ((a) nasal; (b) oral; (c) parenteral; (d) dermal) for antipsychotic delivery. Figure created with Biorender.

Lipid-Based NPs

According to their differences in preparation materials and structures, lipid NPs can be roughly classified into two generations. First-generation lipid NPs, termed as liposomes with a bilayer structure, has a lengthy research history.[105] Liposomes are double-layered hollow vesicles made of cholesterol and phospholipids, and their internal hydrophilic core and lipid bilayer can load hydrophilic and hydrophobic drugs, respectively.[106] Multiple strategies are available for loading drugs into liposomes, including electrostatically adsorbed on liposomal surfaces, directly encapsulated in the lipid bilayer or its hydrophilic core through physical action.[107,108] Liposomes have several benefits, including high biocompatibility and lipophilicity, which makes them easier for cells to absorb. The effectiveness of distribution is also significantly increased by targeted and multifunctional liposomes made by surface modification.[109] Lipid nanoemulsions (LNEs), nanostructured lipid nanocarriers (NLCs), lipid nanocapsules (LNCs) and solid lipid NPs (SLNs), and are the

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several types of lipid NPs that belong to the second generation. They have more stable physical characteristics, greater industrial production opportunities, and a stronger drug-carrying ability for hydrophobic medicines than liposomes.[110]

Lipid-based NPs have been demonstrated to be beneficial for delivering antipsychotic medications (Table 5). Their use has been documented in numerous studies to deliver insoluble antipsychotic drugs like olanzapine,[111] lurasidone,[112] selegiline,[113] and sertraline,[114] resulting in a significant increase in their solubility and bioavailability. Notably, stimuli-responsive liposomes, such as electrically active ferrocene liposomes loaded with carbamazepine that can rapidly react to and release drugs in situ during epileptic discharges, provide inspiration for on-demand drug therapy against antipsychotic diseases.[115]

Previous research has shown that lipid-based NPs can enter the brain through small, highly lipophilic properties without modification or ligand binding.[124–126] The experimental results of Maqsood et al also demonstrated that, in contrast to levosulpiride (LEVO) suspension, LEVO-loaded nano lipid carriers (LEVO NLCs) more effectively crossed the BBB and have advantages in neuroprotection and nerve regeneration, indicating that NLCs can be effectively used for delivering therapeutic agents in the brain.[127] Similarly, lipid NPs administered intranasally can deliver siRNA to the brain, potently relieving depressive-like behaviors caused by LPS.[128]

When combined with other readily available materials, the new lipid NPs can increase the effectiveness of poorly soluble drugs. To increase the solubility and absorption of ziprasidone, for instance, Meola et al created the nano-crystalline silicon lipid hybrid (SLH) particles with an average diameter of 280 nm.[129] The drug loading of SLH was 17 times greater than that of normal SLH microparticles, leading to a significant improvement in the solubility, dissolution, and intestinal absorption of ziprasidone. By combining neutrophils with liposomes, Zhou et al[130] designed a distinctive pharmaceutical delivery approach that exploits the characteristic infiltration of neutrophils into core brain regions during neuroinflammatory responses. To serve as a targeting ligand, they conjugated the N-Acetyl Pro-Gly-Pro (PGP) peptide, which binds effectively to CXCR2 receptors on neutrophil surfaces, onto oxytocin-loaded liposomes (PGP-OTL). This PGP-OTL formulation can "hitchhike" on neutrophils via a novel cell-mediated liposome technique, boosting medication transport to the brain. Thanks to their excellent biocompatibility and lipophilic properties, lipid NPs are particularly valuable for treating mental health illnesses.

Table 5 Example of Lipid NPs for Delivering Antipsychotic Drugs

Carrier Type	Main Composition	Drug	Comments	Ref
NLCs	Acetyl alcohol, Oleic acid, Polysorbate 40, Sorbitan monopalmitate, Polyoxyl 40 stearate	Paroxetine	Paroxetine exhibits 90% encapsulation efficiency, fully entrapping the lipophilic drug and reducing free drug loss.	[116]
	Glyceryl Dibehenate, Oleic acid, Polysorbate 80	Escitalopram	ESC-NLC gel achieved 96% encapsulation efficiency and a 9-fold higher brain drug concentration, significantly improving behavioral outcomes in LPS-induced depressed rats.	[117]
	Glyceryl monostearate, Oleic acid, Polysorbate 80	Buspirone	Chitosan-modified NLCs showed a DTP of 93.16%, significantly higher than the drug solution (81.63%, $p < 0.05$), demonstrating better brain targeting.	[118]
LNCs	Glyceryl caprylate/caprate, Glyceryl Monostearate, Poloxamer 407, Polysorbate 20	Paliperidone	The brain relative bioavailability of PPD-LNCs is 3.46 times that of the drug suspension.	[119]
	Medium Chain Triglycerides, Macrogol (15)-hydroxystearate, Soybean phosphatidylcholine	Mirtazapine	MZP-LNCs exhibit superior brain-targeting capability, delivering significantly more mirtazapine to the brain with a drug targeting efficiency (%DTE) of 332.2%.	[120]
SLNs	Glyceryl monostearate, Stearic acid, Polysorbate 80	Carbamazepine	Intranasal delivery enhanced cerebral carbamazepine penetration versus intravenous injection, reduced oral-related side effects, and the SN1 formulation attained a targeting efficiency of 3.014.	[121]
	Glyceryl Dibehenate, Polysorbate 80, Poloxamer 188	Buspirone (BUS)	BUS-SLNs possess excellent encapsulation and sustained-release properties, and intranasal administration can significantly enhance the brain drug targeting efficiency.	[122]
Liposome	Cholesterol, DSPE-PEG_{2000}-DOCA, EPC, DSPE-PEG_{2000}-R8	Lurasidone hydrochloride (LSD)	p-R8-DOCA-Lipos enhanced LSD loading, provided 3.80-fold higher transepithelial transport, and effectively reduced LSD's food effect.	[112]
	DPPC, Cholesterol, DSPE-PEG_{2000}-biotin, DSPE-PEG_{2000}	Escitalopram	It achieves rapid and sustained elevation of serotonin levels at low doses, effectively improves depression-like behaviors, and overcomes the limitations of conventional oral antidepressant therapy.	[123]

Polymer-Based NPs

Polymeric NPs improve antipsychotic solubility, prolong systemic exposure, and enable sustained release, thus reducing off-target effects and strengthening drug delivery and therapeutic outcomes.[131] In particular, polymersomes formed from amphiphilic block copolymers share a structure similar to liposomes but can be tailored with superior customization through polymer chemistry. They enable on-demand regulation of drug encapsulation properties and membrane permeability, which is crucial for delivering antipsychotic drugs across the BBB while minimizing systemic exposure. Their excellent adaptability enables the co-encapsulation and sustained release of both hydrophilic and hydrophobic antipsychotic drugs, effectively addressing formulation challenges such as poor water solubility and chemical instability.[132,133]

Polymer micelles self-assembled into core-shell nanostructures. The hydrophobic core effectively isolate lipophilic antipsychotic drugs through hydrophobic interactions or covalent bonds, while the hydrophilic corona prolongs drug's systemic circulation time and reduces premature clearance. This architecture optimizes the pharmacokinetic profile and bioavailability of poorly soluble antipsychotic compounds, facilitating improved drug accumulation at target sites within the CNS.[82,134] Dendrimers, characterized by their highly branched three-dimensional architecture, offer multivalent surface functionality enabling efficient drug conjugation and targeted cellular interactions. Cationic dendrimers (eg, polyamidoamine, PAMAM) exhibit strong affinity for cell membranes, promoting endocytosis to facilitate intracellular delivery of nucleic acids. These properties make dendrimers ideal candidate carriers for gene-regulatory therapies targeting psychiatric disorders.[135]

Polymer materials are generally divided into natural materials and synthetic materials according to their origin. Natural polymers including chitosan and hyaluronic acid (HA) are widely used in neuropsychiatric drug delivery systems due to their excellent biocompatibility and multifunctionality.[136] HA offers additional mechanistic benefits due to their inherent biocompatibility and receptor-mediated targeting capabilities.[137] HA-modified NPs can accurately deliver therapeutic drugs to the traumatic brain injury area, thus reducing the off-target effect and improving the therapeutic effect.[138] Consequently, HA may provide inspiration for research on how to deliver antipsychotic drugs to the brain. Moreover, the sensitivity of HA to the enzymatic degradation of HA enzymes in the brain microenvironment makes it possible to stimulate the release of reactive drugs. For example, Ge et al created a multifunctional nanocarrier (AC-RM@HA-MS-KA) that ketamine (KA)-loaded mesoporous silica coupled with HA to act as pore gatekeepers, and coated with red blood cell membranes to evade the immune system. Bifunctional peptides (Ang-2 and Con-G) are applied to the surface to enhance BBB penetration and regional accumulation in the prefrontal cortex and hippocampus, which are crucial areas of mental pathology (Figure 2a). Once localized, endogenous hyaluronidase degrades the HA shell, triggering controlled KA release directly at N-methyl-D-aspartate receptor sites (Figure 2b). This targeted controlled-release system, which exhibits effective BBB crossing and precise brain-directed targeting (Figure 2c and d), greatly reduces the risk of ketamine addiction while maximizing its antidepressant efficacy, illustrating the therapeutic advantages of polymer-based nanocarriers in antipsychotic treatment.[139]

Chitosan has polycationic characteristics because it is rich in amino groups, and can effectively combine with negatively charged biomolecules (eg, nucleic acids, proteins). These amino groups also provide sites for chemical modification, further expanding their application versatility as biological functional materials.[140,141] In the field of psychotropic drug delivery, chitosan is mainly used to prepare hydrogel, and usually uses cross-linking agents such as formaldehyde to achieve a stable structure, so as to build a delivery system with biocompatibility and release control functions.[142] Chitosan-based hydrogels prolong drug retention time within the nasal cavity, enabling sustained release and reducing administration frequency, thus markedly boosting intracerebral drug delivery efficiency. At the same time, this characteristic helps to reduce nasal irritation and improve patient compliance. By co-spraying oxidized starch NPs (SNP-CHO) with carboxymethyl chitosan, Majcher et al developed a biodegradable nanocomposite hydrogel that enhances nasal mucosa adherence and enables sustained release of antipsychotic peptide (PAOPA). Experiments have confirmed that the preparation can penetrate deep into the nasal cavity and form hydrogel in situ, achieve continuous drug release, enhance intracerebral delivery, and effectively control the symptoms of schizophrenia for up to three days.[143] Additionally, hydrophilic chitosan hydrogel can realize the delivery of hydrophobic drugs through reasonable design. Taking the research of Andrew Lofts' team as an example, they oxidized and hydrophobically modified about 20 nanometers of ultra-small starch NPs. Oxidation introduced cross-linkable aldehyde groups, while hydrophobic modification was achieved via conjugation with octenyl succinic anhydride (OSA), yielding amphiphilic SNP-OSA-CHO NPs. Olanzapine was then encapsulated into the hydrophobic core of SNP-OSA-CHO, followed by mixing with

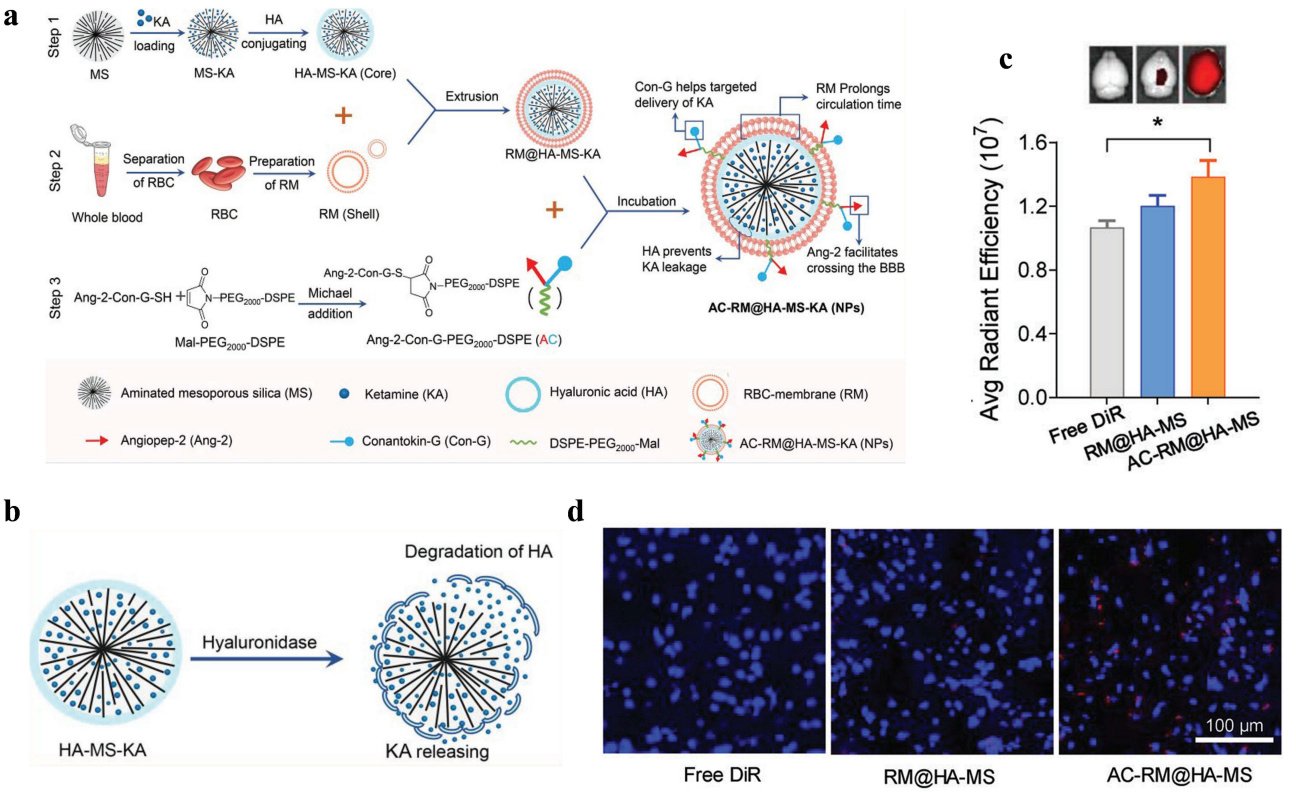

Figure 2 (**a**) Diagrammatic representation of the composition and structure of the AC-RM@HA-MS-KA nanoparticle. (**b**) The mechanism of KA release. (**c**) Ex vivo brain images of depressed mice along with the corresponding average radiant efficiency values (*t*-test, *p< 0.05, n=6). (**d**) DiR-labeled (free/nanosystem-based) confocal fluorescence imaging of frozen brain sections from depressed mice (blue: cell nuclei; red: NPs; scale bar=100 μm). Solid blue arrows indicate directional processes. Reprinted with permission from.[139] Copyright 2023 Wiley.

chitosan oligosaccharide lactate (COL). Through Schiff base-mediated crosslinking, this mixture formed an in-situ hydrogel (SNP-OSA-CHO/COL) (Figure 3a). The hydrogel slowly releases SNP-OSA NPs via cleavage of Schiff-base bonds in the nasal cavity, thereby significantly prolonging olanzapine's antipsychotic effect and overcoming the rapid inactivation of conventional nasal delivery (Figure 3b and c). [144] Chitosan can also be developed into oral formulations. As demonstrated by He et al,[145] TNF-α siRNA and gallic acid–mediated graphene quantum dots were first encapsulated into bovine serum albumin (BSA) via the desolvation method, forming siRNA-GBSA NPs. Subsequently, multiple layers of chitosan and tannic acid (CHI/TA) were assembled on the NP surface through electrostatic layer-by-layer self-assembly—this coating protects the NPs from gastrointestinal degradation, yielding siRNA-GBSA (CHI/TA) n (Figure 3d). This nanosystem not only effectively treated colitis and regulates gut microbiota-brain interactions but also significantly alleviated depressive behaviors in mice, supported by forced swimming test (Figure 3e) and tail suspension test (Figure 3f).

Beyond chitosan, sodium alginate also exhibits considerable potential in drug delivery owing to its favorable biocompatibility and functional tunability.[146] Addressing the key challenges in depression treatment, namely the difficulty of drugs penetrating the BBB and the imbalance of ROS in the brain, Xu et al constructed a ROS-responsive brain-targeted polysaccharide nanogel delivery system (BT-ROS-GA-PA-ANs DDS) based on alginate nanogels (Figure 4). [69] Taking natural sodium alginate as the scaffold, this system loads two natural active ingredients of traditional Chinese medicine, GA and PA. The nanogels were modified with transferrin to achieve BBB targeting, and further formulated into a thermosensitive hydrogel containing collagen to prolong nasal retention. Meanwhile, disulfide bonds were introduced to achieve ROS-responsive controlled drug release in the brain. This design reduces nasal drug loss and improves the antidepressant efficacy. Liu et al utilized other natural polysaccharides such as dextran (DEX) to develop ROS-responsive DEX derivatives modified with hexarginine (R6).[147] These derivatives can load olanzapine and contribute to the treatment of depression through antioxidant effects.

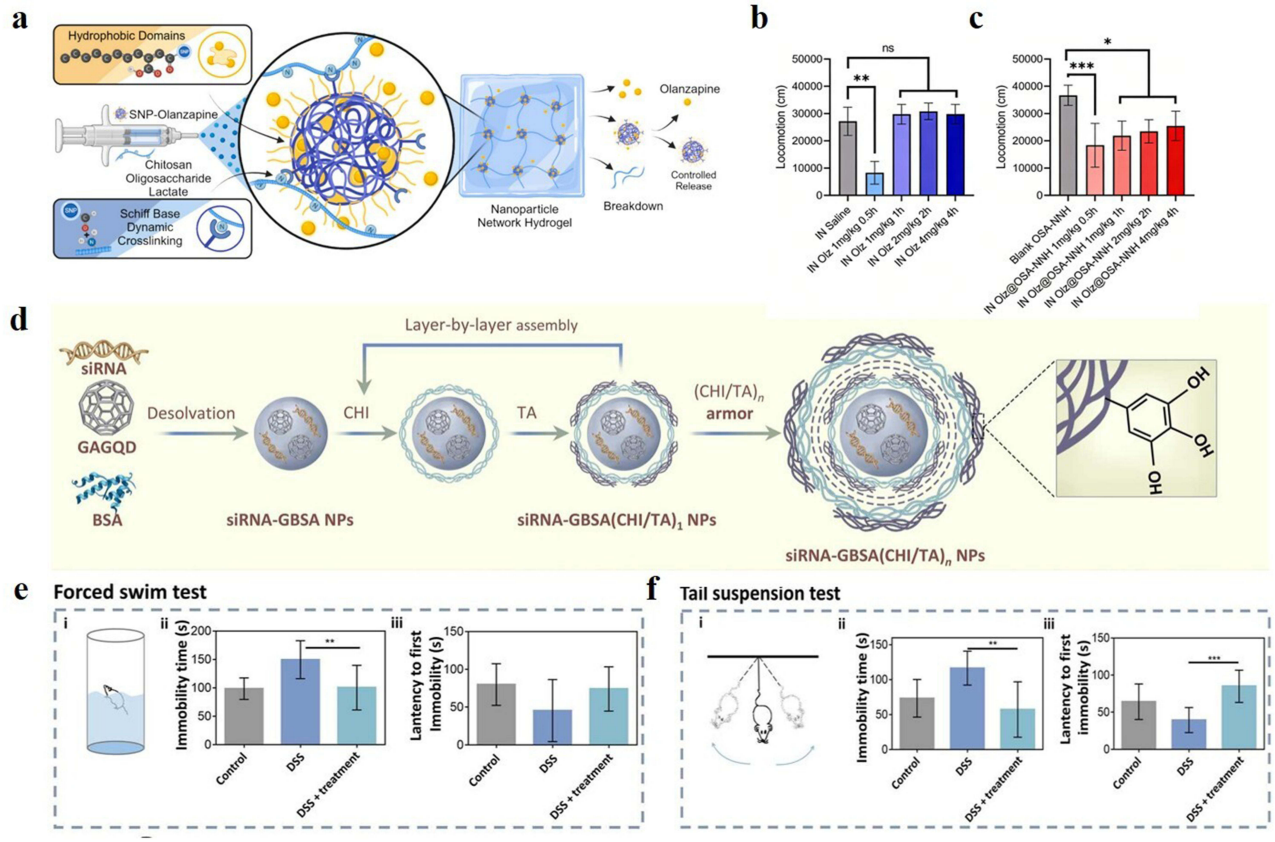

Figure 3 Schematic diagram of chitosan-based nanosystems for ameliorating psychiatric disorders: (**a**) Schematic of design and drug release mechanism for olanzapine-loaded SNP-OSA-CHO/COL in situ gelling nanoparticle network hydrogel. Solid black arrows indicate directional processes. (**b** and **c**) One-hour cumulative locomotion scores in mice receiving amphetamine 0.5–4 h after intranasal administration of either free olanzapine ((**b**) blue) or OLZ@OSA-NNH ((**c**) red) at olanzapine doses ranging from 1–4 mg/kg. One-way RM ANOVA with Dunnett's test, *p < 0.05, **p < 0.01, ***p < 0.0005; ns, not significant, n=6. Reprinted with permission from.[144] Copyright 2024 Elsevier. (**d**) Synthetic scheme of siRNA-GBSA (CHI/TA) n NPs. Blue arrows denote material assembly. (**e**) Forced swimming test: (i) Schematic diagram; (ii) immobility time; (iii) latency to first immobility; (**f**) Tail suspension test: (i) Schematic diagram; (ii) immobility time; (iii) latency to first immobility. One-way ANOVA with Tukey's test, **p < 0.01, ***p < 0.001, n=10. Reprinted with permission from.[145] Copyright 2023 AAAS.

Chemical techniques like reversible addition breakage chain transfer[148] and reversible deactivation radical polymerization[149] allow for flexible structural modification of produced polymers, which can be utilized to create polymer-drug conjugates, multiblock copolymers, and other materials. This enhances drug loading and provides a wide development platform for the creation of polymer nanocarriers by enabling the screening of corresponding structures from a large chemical library and using their charge, amphiphilicity, responsiveness, and other properties to achieve controlled drug release and improve drug safety.[150,151]

Currently, widely studied or commercially available polymers are frequently employed to deliver psychotropic drugs due to their established safety profiles (Table 6).

Biodegradable polymer NPs represent a promising nanoplatform for antipsychotic drug delivery due to their ability to enhance drug solubility, membrane permeability, and bioavailability, while simultaneously reducing systemic toxicity. Notably, polymers synthesized through amino acid polymerization—which resemble natural proteins in structure and functio—exhibit excellent biocompatibility, biodegradability, and low immunogenicity.[155] Lugasi et al successfully encapsulated RSP within protein-mimetic polymer NPs, designated prot1/RSP and prot2/RSP. To enhance the formulation's in vivo stability, they prepared RSP-loaded protein NPs via PEGylation following RSP-mediated self-assembly. Compared with free RSP, prot.1/RSP and prot.2/RSP exhibited better solubility, stability, and brain-targeting ability, suggesting their potential as efficient nanocarriers for CNS drug delivery.[156] Polydopamine (PDA) is a typical synthetic biopolymer that has a straightforward preparation method and excellent biosafety and ROS scavenging abilities, which can reduce inflammation in the inflammatory microenvironment.[167] To alleviate depression, Jiang et al created an inflammation-targeting microglial-biomimetic system (PDA-Mem@M) to eliminate

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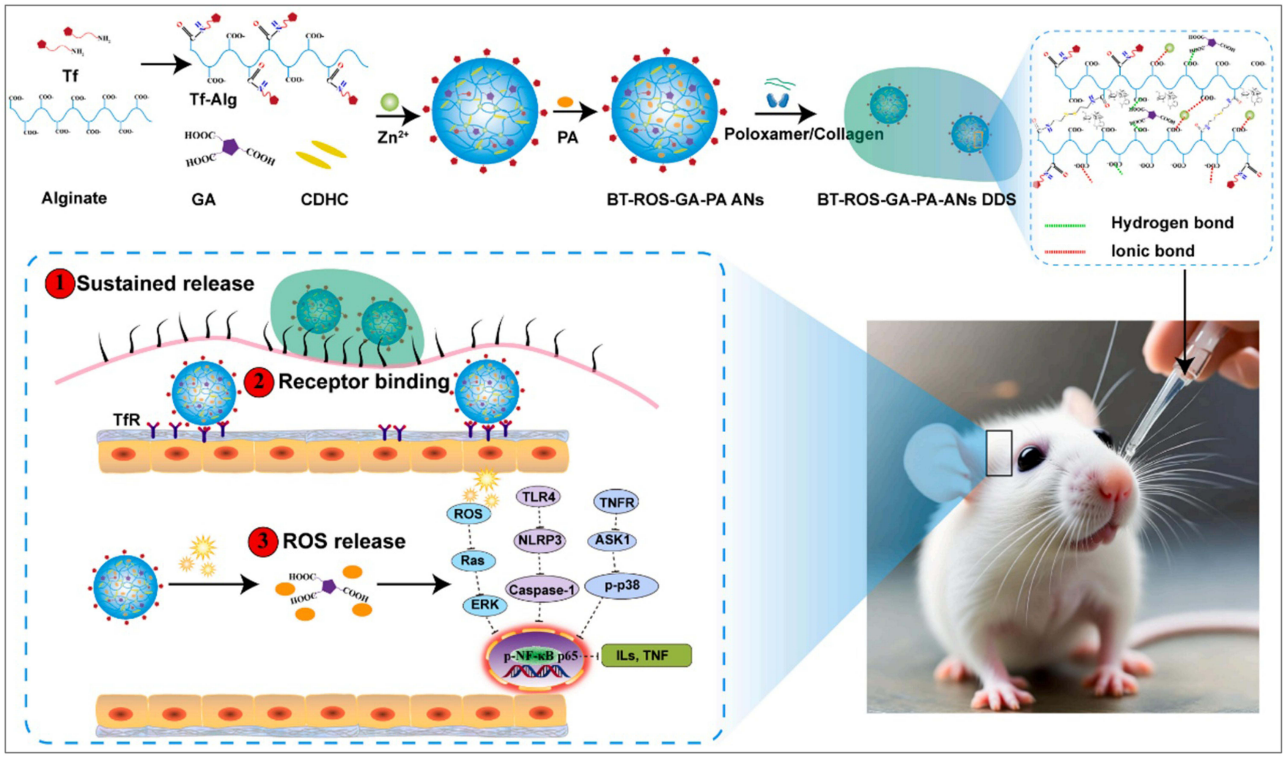

Figure 4 Design and antidepressant mechanism of brain-targeted, ROS-responsive polysaccharide nanogels. Red circled numbers (①, ②, ③) indicate the sequential steps of the nanogel delivery process, including sustained release, receptor binding, and ROS release. Solid black arrows show the directional processes; dashed arrows denote the sequential activation of intracellular signaling pathways; green and red lines represent hydrogen and ionic bonds, respectively. Reprinted with permission from.[69] Copyright 2025 Elsevier.

ROS and upregulate BDNF expression.[168] PDA-Mem@M, engineered with a BV2 cell membrane shell derived from microglia and a Mem-loaded PDA core, exhibits the multi-capabilities of penetrating the BBB to target microglia, alleviating the inflammatory environment via PDA-mediated ROS elimination, and enabling pH-responsive Mem release. Experimental results

Table 6 Example of Polymer NPs Used for Delivering Psychotropic Drugs

Drug	Materials	Psychiatric Disorder	NPs	Ref
Aripiprazole	Polyvinyl caprolactam-polyvinyl acetate-PEG graft copolymer and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)	Schizophrenia	ARP-MM	[152]
	Poly (methyl vinyl ether-co-maleic anhydride) (PVMMA)	Depression	PA NPs	[153]
Paliperidone	TPGS	Short-term psychotic management	PPTPGS	[154]
RSP	l-glutamic acid, l-phenylalanine and l-histidine, poly (l-lactic acid) and PEG	Schizophrenia and Bipolar disorder	P(EFH-PLLA)/RSP	[155]
	l-amino acids and poly-l-lactic acid	Schizophrenia	Prot.1/RSP and Prot.2/RSP	[156]
	Hydroxypropyl-beta-cyclodextrin (HPβCD)	Autistic mood swings, Bipolar disorder and Schizophrenia	HPβCD/RSP-IC nanofibers	[157]
Buspirone	Thiolated chitosan	Anxiety disorder	TCS-NPs	[158]
Quetiapine fumarate	Chitosan	Schizophrenia	QF-NP	[159]
Haloperidol	PEG–PLGA	Schizophrenia	Haloperidol-loaded, STL-functionalized PEG–PLGA NPs	[160]
Haloperidol	PAMAM	Schizophrenia	D-HP	[161]
Clozapine	Poly-l-lysine (PLL) and Poly-l-glutamic acid (PGA)	Schizophrenia	CLO-NCs	[162]
	PGA-g (39)-PEG	Schizophrenia	CLO-NCs	[163]
	Polycaprolactone (PCL)	Schizophrenia	CLO-PCL NPs	[164]
Clozapine and RSP	PLGA	Schizophrenia	_	[165]
Olanzapine and H_2 donor amino borane	R6 modified ROS-responsive DEX derivate	Depression	Olz/RDPA NPs	[147]
Desvenlafaxine	PLGA-chitosan	Depression	DVF PLGA-CN NPs	[166]

show that this nanosystem has excellent brain targeting ability and ROS scavenging capacity, and exhibits a good therapeutic effect in mice with chronic restraint stress-induced depression (Figure 5).

The solubility of poorly water-soluble drugs can be significantly enhanced by nanoscale co-precipitates formed through drug nucleation facilitated by polymers. PVMMA copolymer finds broad application as a drug carrier for its bioadhesive property and ability to react with various functional groups to build multifunctional delivery systems.[169] Chen et al prepared composite NPs (PA NPs) of aripiprazole and PVMMA using an environmentally friendly fluid method. Compared to free aripiprazole, PA NPs treatment significantly lowered serum inflammatory marker levels and attenuated microglial activation in LPS-induced mouse brains. According to mouse behavior tests, PA NPs significantly alleviated the depressive-like behavior induced by LPS.[153]

Polymer-based delivery systems offer numerous advantages, including precise targeting and controlled drug release triggered by internal or external stimuli.[92] Building on these observations, polymers emerge as exceptionally promising drug delivery vehicles, facilitating the creation of customized NPs for efficient antipsychotic administration.

Inorganic Nanomaterials

Nanoenzyme-Based NPs

Nanozymes are synthetic catalysts that mimic the biocatalytic activity of natural enzymes. These materials excel in biocatalytic applications because they offer greater stability, better scalability, and lower costs than natural enzymes.[170,171] In fields like tumor therapy and diagnosis,[172] as well as regenerative medicine,[173] nanozymes have gained growing traction—they combine the catalytic specificity of natural enzymes with the multifunctional properties of

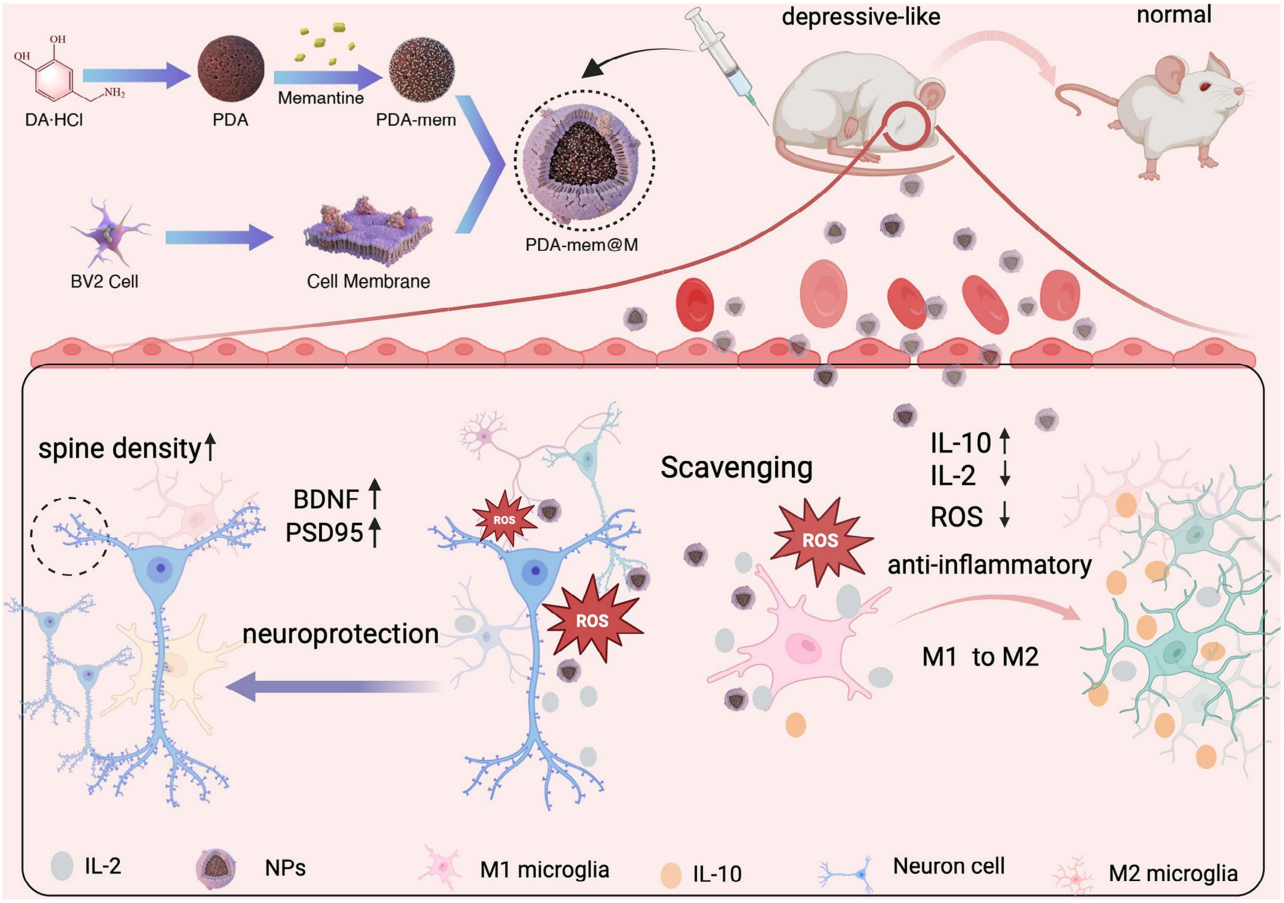

Figure 5 Schematic diagram showing the synthesis process of PDA-Mem@M and its regulatory effect on neuroinflammation and neuroplasticity in depression. Solid blue arrows indicate directional processes; curved arrows denote administration, state transition, and microglial polarization; upward/downward arrows indicate increased/decreased levels. Reprinted with permission from.[168] Copyright 2025 Wiley.

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nanomaterials. These functional features, together with their compact size and antioxidant capacity, further suggest strong potential for addressing psychiatric disorders. Singh et al reported on a cerium vanadate (CeVO4) nanoenzymes with high superoxide dismutase (SOD) activity. These nanoenzymes can functionally replace SOD1 and SOD2 in nerve cells, help regulate the level of intracellular superoxide, restore levels of anti-apoptotic Bcl-2 family protein, and protect neurons from oxidative damage.[174] Therefore, CeVO4 nanozymes are expected to compensate for the defects in neuronal SOD function in psychiatric disorders, reverse abnormal mitochondrial energy metabolism and inhibit neuronal apoptosis. It is a potential new nanotherapeutic that intervenes in psychiatric disorders. The CeO2@BSA nanocluster synthesized with BSA as the template, with its ultra-small structure of about 2 nanometers, has high-efficiency BBB penetration, rapid in vivo metabolic clearance and excellent active oxygen removal ability. It verified the antidepressant-like effect of the nanocluster in a chronic restraint stress-induced depression model, which provided a reference for the development of nanoenzyme-based neuropsychiatric disease treatment.[175] For inorganic materials used in antidepressant treatment, some work through nanoenzyme activity, while others improve the therapeutic effect through carrier function. Shi et al developed an N-acetylcysteine (NAC)-sealed gold nanocage for loading TLQP21. In an oxidative stress environment, TLQP21 is released upon consumption of NAC. This system effectively attenuates oxidative stress in the mouse brain and ameliorates major depressive disorder. In this study, the gold nanocage did not use its inherent nanoenzyme potential, but realized the ROS response release of TLQP21 as a drug carrier, thus providing practical support for the wide application of inorganic materials in this field.[176]

BP Nanosheets

BP nanosheets is a two-dimensional material with a large specific surface area, which have garnered significant attention owing to their biodegradability into non-toxic phosphorus oxides and favorable optical properties. These characteristics make BP nanosheets suitable for biomedical applications, especially photodynamic therapy and photothermal treatment.[177,178] BP nanosheets can enhance the permeability of the BBB through near-infrared (NIR)-irradiated photothermal mediation. This characteristic gives them a potential application in the treatment of psychiatric disorders.[179] Wang et al used BP nanotaphets coated with fluoxetine (BP–Flu) to study its potential to treat depression. They further developed a BP-based photothermal combined chemotherapy drug co-medication platform, providing a synergistic strategy to enhance the efficacy of antidepressant (Figure 6a). Fluorescence imaging confirms that BP nanosheets boost the BBB via the photothermal response. Importantly, in the behavioral test, BP-Flu combined with 808 nm laser irradiation can produce faster antidepressant response and lower toxicity than fluoxetine alone.[180]

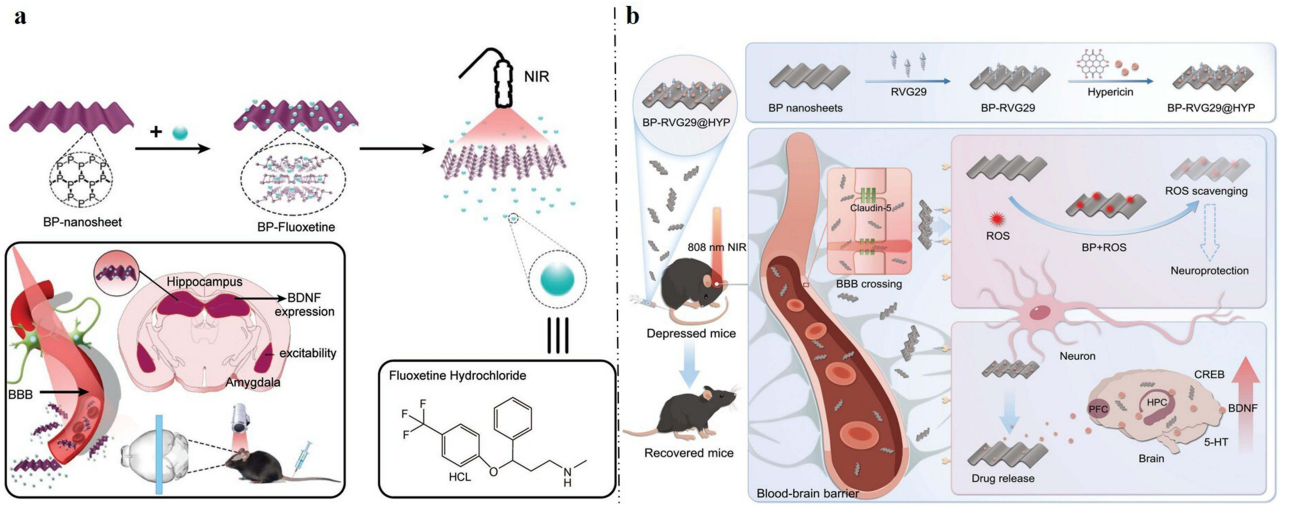

Figure 6 (**a**) Schematic diagram of BP NPs for synergistic photothermal/chemotherapy treatment of depression. Solid black arrows indicate directional processes. Reprinted with permission from.[180] Copyright 2020 Wiley. (**b**) Brain-Targeted based on BP-RVG29@HYP for nanotherapy. Red arrows show the upregulation of 5-HT, BDNF, and CREB; blue arrows indicate the directional processes; the dashed arrow denotes the indirect neuroprotective effect. Reprinted with permission from.[181] Copyright 2024 Wiley.

Excessive ROS can cause oxidative stress, resulting in cell damage and functional imbalances associated with psychiatric disorders.[182,183] BP nanosheets possess ROS-scavenging ability due to their unique molecular structure and can serve as drug carriers.[184] Therefore, they are expected to exert antidepressant effects by reducing oxidative stress. Tan et al developed a low-toxicity BP nanoplatform for efficient delivery of the natural antidepressant medication hypericin (HYP) to the brain. Specifically, they developed a nano-platform, BP-RVG29@HYP (BRH), by loading the natural antidepressant HYP onto BP functionalized with the neural cell-targeting peptide RVG29. BRH specifically targets acetylcholine receptors and crosses the BBB via endocytosis by cerebral capillary endothelial cells. Upon 808 nm NIR irradiation, BRH significantly down-regulates Claudin-5, a tight junction protein involved in maintaining BBB integrity, thereby enhancing BBB permeability. Once in the brain, BRH exerts dual antidepressant effects by scavenging ROS through BP nanosheets and modulating neurotransmitter function, including 5-HT, via HYP release (Figure 6b). [181]

Graphene Oxide (GO)

GO, an oxidized graphene-derived product, exhibits enhanced hydrophilicity and provides outstanding loading capability for both hydrophilic and hydrophobic drugs.[185,186] Torabi Fard et al developed a targeted delivery system for venlafaxine by loading it onto GO modified with a polyester dendrimer and adorned with 3,4-dihydroxybenzoic acid.[187] Additionally, GO has been reported to exhibit intrinsic neuroprotective properties, which may contribute to the prevention or attenuation of depression.[188,189] Yu et al developed a PEG-modified GO nanocarrier (GO-PEG-BO) functionalized with borneol (BO) and loaded with ginsenoside Rg1 (GRg1). BO serves as a targeting and permeation enhancer, temporarily and reversibly opening the BBB and inhibiting efflux mechanisms, thereby facilitating efficient GRg1 delivery to the brain without causing significant neural damage. GRg1/GO-PEG-BO exhibits uniform particle size (179.21 ± 1.95 nm), good dispersibility (PDI 0.272 ± 0.028), and enables sustained and complete release of GRg1. Upon intravenous administration, the nanocarrier successfully crossed the BBB with the assistance of BO and delivered GRg1 to the brain (Figure 7). Notably, GO itself can improve depression-related neuroplasticity abnormalities by upregulating the expression of neurotrophic factors such as NGF and BDNF. This property remains stable after PEG and borneol modification, synergizing with the antidepressant effects of GRg1 to further enhance therapeutic efficacy.[190]

Superparamagnetic Iron Oxide NPs (SPIONs)

SPIONs are composed of magnetic iron cores (such Fe_3O_4 or Fe_2O_3) and are typically coated with biocompatible materials. They exhibit strong paramagnetism, nanoscale dimensions, and functionalizability, making them ideal

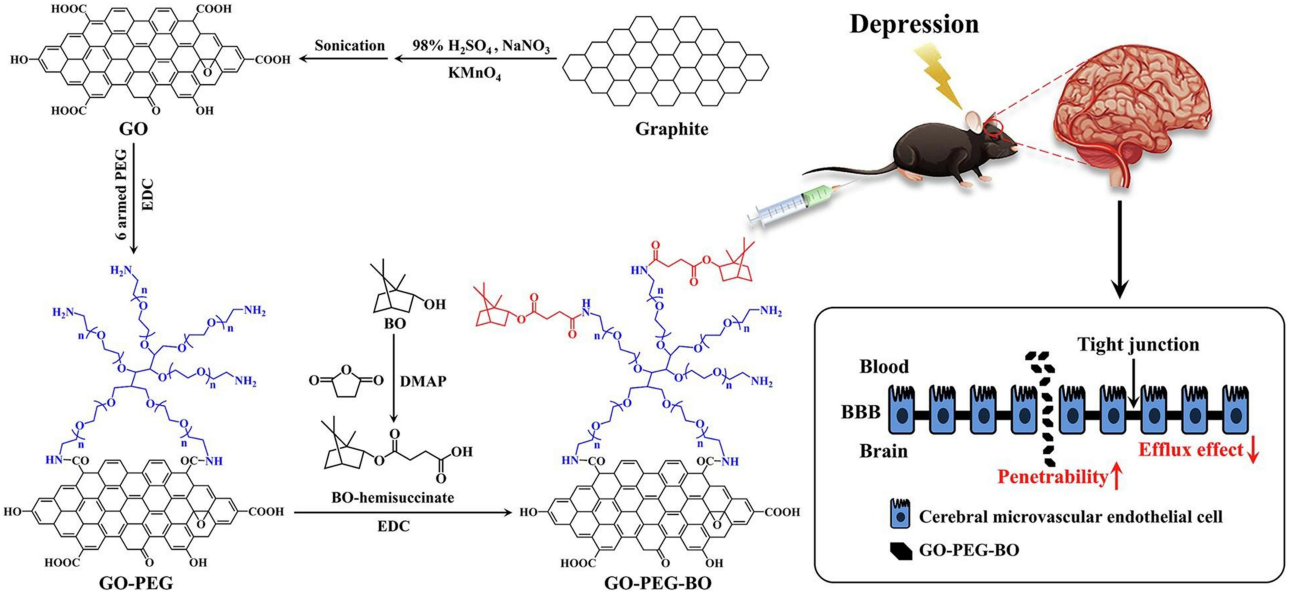

Figure 7 Schematic diagram of the fabrication and BBB translocation of GO-PEG-BO. Solid black arrows indicate directional processes; red upward/downward arrows indicate increased/decreased levels. Reprinted with permission from.[190] Copyright 2023 Elsevier.

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candidates for biomedical applications. SPIONs have been extensively used as contrast agents in nuclear magnetic resonance imaging (MRI) due to their excellent magnetic properties. SPION-based nanocarriers have been explored to deliver drugs across the BBB, improve brain accumulation, reduce peripheral side effects, and support real-time visualization of drug distribution via MRI.[191] Notably, the magnetic response properties of SPIONs can also synergize with neurostimulation technologies to exert therapeutic effects, providing an innovative treatment strategy for psychiatric disorders. Afshari et al directly injected SPIONs into the lateral ventricles of the brain followed by continuous application of low-frequency repetitive transcranial magnetic stimulation for 14 days in a valproic acid-induced ASD rat model.[192] This combined therapy successfully reversed ASD-related behavioral abnormalities (such as increased anxiety and repetitive behaviors) while simultaneously reducing levels of relevant factors like BDNF, MAP2, and SYN, which offers a novel therapeutic strategy for ASD treatment. SPIONs can be chemically modified to enable nanoscale strategies for controlled release and targeted drug delivery. Fang et al engineered chitosan-functionalized Fe_3O_4 NPs (Fe_3O_4@CS) through an in-situ serotonin synthesis strategy (Figure 8a). These nanozymes can catalyze the conversion of tryptophan into 5-hydroxytryptophan, effectively compensating for the impaired activity of tryptophan hydroxylase and promote the release of presynaptic neurotransmitters in the brain. This approach offers a more targeted and efficient means of restoring serotonin levels, thereby offering a hopeful therapeutic solution for treating depression.[193] Through amidation condensation, Wang et al conjugated amino-modified Fe_3O_4 to the outer membrane of engineered bacteria, taking advantage of its magnetothermal conversion trait to regulate GABA release. After oral administration, the poly(norepinephrine) layer enhanced the mucosal adhesion of genetically engineered Escherichia coli Nissle 1917 (EcN). The Fe_3O_4 layer converted magnetic stimulation into local heat, which triggered temperature-dependent GABA release from the genetically engineered EcN (Figure 8b). [194] The gut-brain axis can be regulated effectively and controlled by this nano-assisted engineered bacterial system, and it has the potential to be used in therapy to relieve anxiety. Those approaches offer improved spatial targeting, deeper penetration, and enhanced focusing accuracy, suggesting that SPION-based neuromodulation may evolve into a robust approach for the precise management of psychiatric disorders.

Inorganic-Organic Hybrid Materials: MOFs

MOFs constitute a family of crystalline materials that are coordinated by metal ions or clusters and organic linkers, possessing well-defined porous structures with tunable characteristics.[195] The delivery scope of deliverable therapeutic substances can be significantly expanded by efficiently loading traditional small-molecule drugs and special therapeutic agents, such as carbon monoxide.[196,197] They also show special utility in the management of neuropsychiatric disorders. Many obstacles have long hampered the clinical treatment of conditions like depression and schizophrenia, such as the difficulty of crossing the BBB, inadequate drug targeting, intricate pathogenic pathways, and the potential for drug addiction. Particularly in the fields of multi-target synergistic therapy and precision drug delivery, MOFs provide creative answers to these constraints.

To develop a MOFs-based drug delivery system for psychiatric disorder treatment, Hu et al utilized carbonized frameworks (CFs) derived from MIL-100 (Fe). The resulting platform (CFs@DP) serves as an intranasal delivery system and features dual response to NIR light and magnetic signals (Figure 9a–c). [198] The porous structure and iron-based composition of MIL-100 (Fe) give it a dual-functional basis. On one hand, the porous framework provides ample space for drug loading, enabling the efficient encapsulation of domperidone (DP) with a drug loading efficiency of approximately 12.5–14.3%. On the other hand, the iron-based component not only confers excellent paramagnetism to the material (saturation magnetization reaching 84.42 emu g^{-1}) but also serves as a cerebral iron supplement, participating in dopamine receptor (DR) synthesis and tyrosine hydroxylase (TH) activity regulation, which aligns with the crucial role of cerebral iron metabolic balance in mental function. During the treatment phase (Figure 9d), DP released by CFs@DP acts dually on synaptic membranes: it binds to presynaptic D_2 receptors to boost dopamine storage, recycling and release, and to promote dopamine-D_1R binding, thereby activating the AC/cAMP/CREB pathway and increasing BDNF expression to produce antidepressant-like effects. After drug withdrawal (Figure 9e), the CFs@DP induces upregulation of the CaMKII/CREB/BDNF axis, modulating synaptic plasticity and further elevating BDNF levels. This approach eases depressive/cognitive symptoms safely without addiction risk.

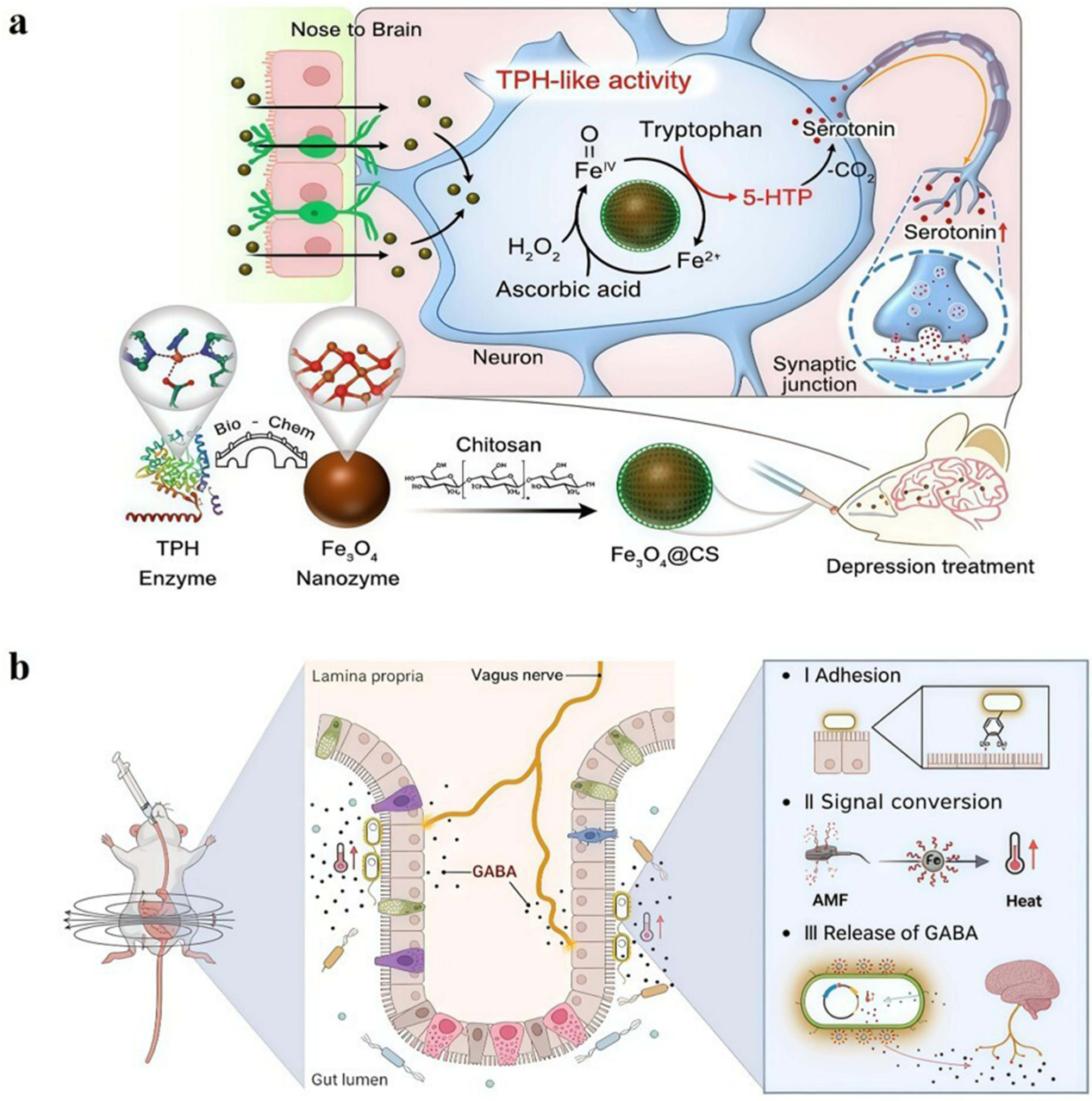

Figure 8 (**a**) The schematic representation of how a tryptophan hydroxylase (TPH)-like nanozyme can restore serotonin synthesis in neurons to treat depression. Solid black arrows indicate directional processes; red curved arrow denotes the catalytic reaction of tryptophan to 5-HTP; red upward arrow indicates increased serotonin levels. Reprinted with permission from.[193] Copyright 2025 ACS. (**b**) Schematic illustration of the mechanism by which EcN-GadABC@Fe-NE modulates anxiety-like behaviors through the Gut-Brain Axis. Solid black arrows indicate directional processes; red upward arrows indicate increased levels; curved arrows denote signaling pathways. Reprinted with permission from.[194] Copyright 2025 BMC.

In addition, the light-responsive UZPM system, carried by ZIF-8, is delivered into live macrophages via functional liposome fusion and is further surface-modified to form the CAR-M-UZPM delivery platform. Leveraging CTLA-4 to target central M1-type microglia, it releases melatonin under NIR light stimulation, regulates microglial polarization balance, and inhibits neuroinflammation, thus providing an efficient central immune regulation strategy for inflammation-related depression.[66] These two MOFs-based delivery systems, proceeding from the two pathways of neurotransmitter regulation and central anti-inflammation respectively, overcome the core bottlenecks of difficult drug delivery and poor targeting in neuropsychiatric disease treatment, fully demonstrating the unique advantages and broad application prospects of MOFs in this field.

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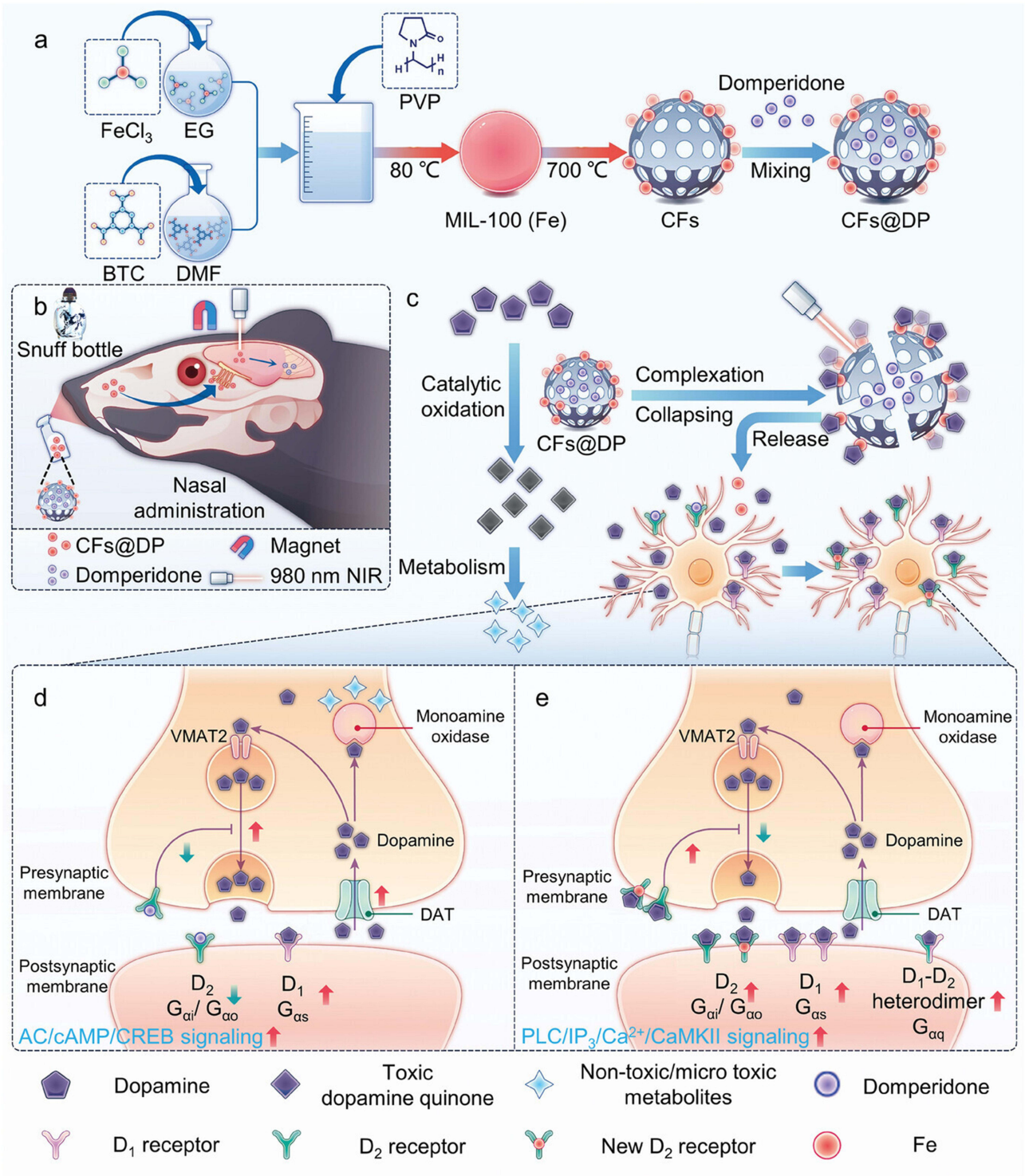

Figure 9 Schematic diagram of CFs@DP application in magnetic targeted drug delivery and neural therapy. (**a**) Synthesis of CFs@DP. Blue arrows indicate the addition of raw materials ($FeCl_3$, BTC, PVP, and domperidone), and red arrows represent the key fabrication processes of CFs. (**b**) Snuff bottle-derived magnetic targeted intranasal delivery platform for CFs@DP. (**c**) Mechanisms of toxicity attenuation and controlled drug release. (**d**) Therapeutic mechanism during drug administration. (**e**) Therapeutic mechanism after drug withdrawal. Solid colored arrows indicate directional processes; curved arrows denote signaling pathways; red upward and green downward arrows indicate increased/decreased levels. Reprinted with permission from.[198] Copyright 2024 Wiley.

EVs

EVs are nanoscale, phospholipid bilayer-enclosed particles that mediate intercellular communication in vivo. They are derived from various cell types, including exosomes and microvesicles.[199,200] Owing to their endogenous origin, EVs exhibit high biocompatibility and stability in circulation, making them resistant to rapid degradation by the immune system.[201]

EVs also exhibit intrinsic targeting capabilities and the ability to cross the BBB, as demonstrated in recent studies.[202] In specific therapeutic trials, EVs have demonstrated a favorable safety profile in humans and possess several key characteristics of an ideal drug delivery carrier.[203] It is worth noting that clinical translation of EV-based therapies largely depends on advancements in isolation technologies and the development of improved strategies to control their biodistribution in vivo. Therefore, delivery efficiency can be enhanced by engineering with targeting properties. Yu et al[204] developed RVG-modified EVs loading the circular RNA circDYM (RVG–circDYM EVs), leveraging the natural ability of EVs to protect endogenous bioactive molecules and cross the BBB. RVG specifically targets acetylcholine receptor, enabling efficient EV-mediated delivery of circDYM to the brain. Mechanistically, circDYM binds to the transcription factor TAF1 to downregulate its downstream target genes, thereby suppressing CNS inflammation and effectively alleviating depressive-like behaviors. This work is effective in treating severe depression and has potential for clinical application. Wang et al, created PBGE (Figure 10a), a Prussian blue (PB) nanodrug system encapsulated in macrophage exosomes and loaded with geniposide (GEN).[205] Benefiting from the excellent biocompatibility and low immunogenicity of exosomes, as well as the specific

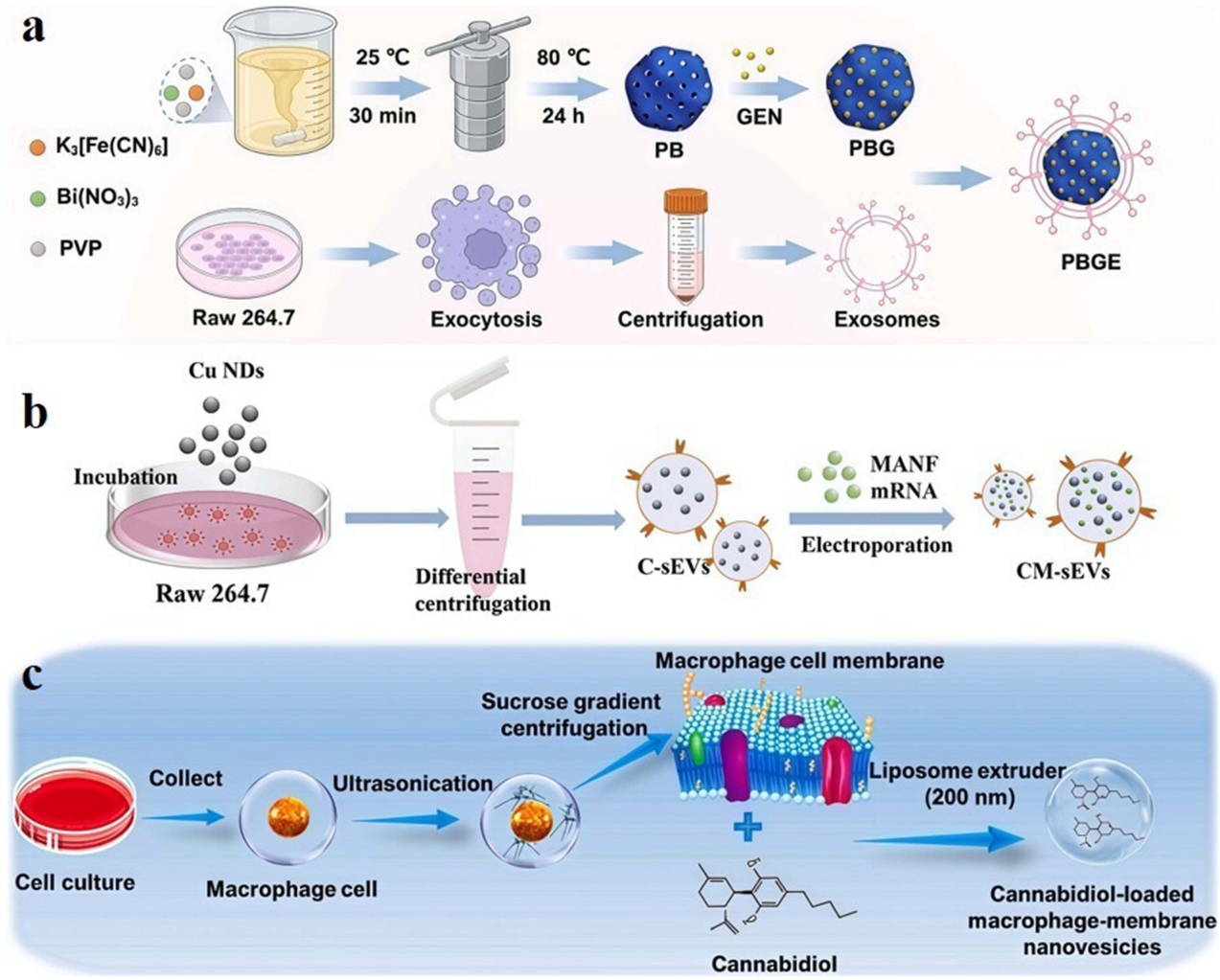

Figure 10 Schematic synthesis of (**a**) PBGE (Reprinted with permission from.[205] Copyright 2025 Wiley); (**b**) CM-sEVs (Reprinted with permission from.[206] Copyright 2025 Wiley); (**c**) CMNV nanodrugs (Reprinted with permission from.[207] Solid blue arrows indicate directional processes. Copyright 2023 Elsevier).

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interaction between exosomal LFA-1 and ICAM-1 on cerebral vascular endothelial cells, this system significantly enhances BBB penetration efficiency and improves targeting to inflammatory brain sites. In addition to enhancing the bioavailability of GEN as a carrier, PB also eliminates ROS accumulated in the brain. The interaction between GEN and PB activates the Nrf2-ARE signaling pathway, enhancing the body's resistance to oxidative stress. This significantly improves depressive-like behaviors by further inhibiting microglial activation, lowering inflammatory markers like IL-1β and IL-6, and restoring synaptic plasticity and neurogenesis. Another innovative study constructed a bifunctional engineered EVs system, CM-sEVs.[206] By co-incubating Raw 264.7 cells with copper nanodots (Cu NDs) and isolating Cu ND-loaded C-sEVs via differential centrifugation, MANF mRNA was further loaded through electroporation to form CM-sEVs with both gene delivery and enzymatic activities (Figure 10b). Utilizing EVs' ability to cross the BBB and target microglia, the system enables Cu NDs to scavenge intracellular ROS for maintaining mitochondrial homeostasis, and MANF mRNA to inhibit the NF-κB pathway after translation. Ultimately, it promotes microglial M2 polarization, downregulates pro-inflammatory cytokines, and significantly alleviates LPS-induced depressive-like behaviors. Moreover, for treatment of post-traumatic stress disorder (PTSD), bionic EVs also demonstrate unique value. Qi et al[207] loaded cannabidiol into macrophage-derived vesicles (CMNVs) and enhanced delivery efficiency by leveraging the inflammatory targeting and immune evasion properties of the macrophage membrane (Figure 10c).[207] With ultrasound assistance, this system further enhances BBB permeability, targets inflammatory brain regions, and effectively alleviates PTSD symptoms. These studies, through the synergistic design of enzyme-mimetic nanomaterials and EVs, offer a novel targeted therapy for inflammation-related psychiatric disorders, further highlighting the clinical potential of EVs in this field.

Challenges in Clinical Translation

While nanoparticle delivery systems can improve the solubility, bioavailability, and targeting of antipsychotic drugs, they still face significant challenges in clinical translation. Two major bottlenecks stand out. First, our understanding of nano-bio interactions in complex pathological environments is limited, which affects how NPs distribute, metabolize, and work in vivo. Second, nanomedicines for psychiatric disorders encounter general barriers during clinical development, including incomplete safety evaluation, a lack of unified regulatory standards, and limited scalability for large-scale production.

Major in vivo Microenvironmental Challenges for Nanoparticle Brain Delivery

The BBB stands out as a key obstacle for delivering drugs to the psychiatric disorders because it tightly controls which molecules and cells can enter the brain. For systemically given NPs to reach their target brain regions, they need to stay stable in the circulatory system and cross the BBB successfully. A major issue during systemic circulation is the clearance of these NPs by the mononuclear phagocyte system (MPS), which is predominantly localized in the liver and spleen. Nanoparticle size is a critical determinant of their in vivo behavior: particles smaller than 6 nm are rapidly filtered by the kidneys, whereas those exceeding 200 nm are preferentially sequestered by the MPS. Particles in the 10–200 nm range, particularly 10–100 nm, represent an optimal window for prolonged circulation and effective lymph node access.[208,209] Besides size, the surface properties of NPs also have a notable impact on how they interact with blood proteins and immune cells. When these particles enter the bloodstream, they bind to serum proteins to form a protein corona. This corona is able to mask the targeting ligands on the surface of NPs and accelerate immune system clearance, which in turn diminishes therapeutic efficacy.[210,211] To tackle these problems, researchers have widely used surface modification methods like PEG grafting, also known as PEGylation, to create stealth coatings. These coatings reduce protein adsorption and help NPs stay in circulation longer.[212,213] The recent innovative strategy aims to actively customize the composition of the protein crown, improve the targeting specificity by designing its components, and effectively transform the crown from biological barriers into functional advantages. For instance, researchers have demonstrated that chitosan NPs loaded with siRNA and encapsulated in BSA modified with cyclic RGD can enhance delivery efficiency.[214] These "nanoparticle stealth" technologies provide valuable insights for optimizing nanoformulations used in psychiatric disorder treatment, as prolonging in vivo drug circulation time and achieving precise targeting are indispensable in this field.

Insufficient accumulation of therapeutic drugs in target brain regions or specific target cell types constitutes another major drawback. Protein coats tend to mask surface ligands on NPs, a process that reduces receptor-mediated recognition efficiency at the BBB and leads to non-specific distribution throughout the brain. Even NPs that successfully traverse the BBB often lack

the ability to selectively localize to diseased subregions or specific cell populations within the CNS. To address this challenge, multi-tiered targeting strategies have emerged as a viable solution. For instance, Ge et al developed a dual-targeting cascade system where Ang-2 promotes BBB crossing, while Con-G enables targeting of lesion sites. Such cascade systems boost the site-specific accumulation of therapeutic agents, which in turn improves treatment outcomes for psychiatric disorders.[139]

Safe Manufacturing Considerations for Translating Nanoparticle Brain Delivery to Clinical Use

Multiple hurdles impede the clinical translation of nanomedicines, including non-standardized safety/toxicity assessment systems, ambiguous regulatory pathways, and poor reproducibility in large-scale manufacturing. Although optimally designed NPs theoretically offer controlled release and targeting capabilities, a comprehensive preclinical and clinical evaluation of parameters including cytotoxicity, immunotoxicity, and genotoxicity is required before they can enter clinical use—particularly for newly developed nanomaterials.[215] Additionally, nanoparticle accumulation in the CNS poses a risk of neurotoxicity and long-term effects like aggravated anxiety, a risk that should not be ignored.[216]

From the perspectives of risk control and research efficiency, standardized in vitro evaluation has become a critical step in preclinical research for brain-targeted nanodelivery systems after basic physicochemical characterization. In current studies, microfluidic models, 2D Transwell co-culture models, and 3D organoid models are commonly used to mimic the BBB. Based on measurements such as trans-endothelial electrical resistance (TEER) and nanoparticle permeability coefficients, these models enable efficient assessment of BBB penetration, cellular uptake efficiency, and biosafety of the delivery vehicles.[217]

A well-established in vitro evaluation system not only enables rapid screening of optimal formulations and targeting strategies, but also provides in-depth insights into the intrinsic mechanisms of nanoparticle transport across biological barriers. It thereby offers reliable scientific support for subsequent in vivo experiments and enhances the reliability and reproducibility of research outcomes. Without such standardized assessment, in vivo behavior becomes unpredictable, leading to poor reproducibility, higher costs, and lower translation efficiency.[218,219]

To meet clinical application requirements, appropriate sterilization methods must be selected for nanomedicines based on the characteristics of the carrier material and formulation. Sterile filtration (0.22 μm) works under mild conditions and has little effect on particle size or drug loading, making it particularly suitable for heat-sensitive or structurally sensitive brain-targeting nanosystems. However, it is only applicable to NPs smaller than the pore size of the filter membrane and is prone to pore blockage, which affects efficiency and yield. Autoclaving is efficient and inexpensive, which suits stable systems like inorganic metal NPs. But the high heat and pressure can compromise the structural integrity of organic carriers (eg, polymers), leading to aggregation or degradation.[220] Ionizing radiation (eg, γ-rays) kills microorganisms thoroughly, yet high doses may degrade carriers and damage drugs—thus it is unsuitable for heat-sensitive materials.[221] Non-ionizing radiation (eg, ultraviolet) is easy to use but penetrates poorly, limiting it to surface sterilization.[222] In short, the sterilization process must be carefully aligned with the carrier material, formulation, and targeting strategy to preserve uniform particle size, stable drug loading, and effective brain targeting.

Despite the excellent BBB penetration and lesion accumulation capabilities of brain-targeted nanomedicines in preclinical studies, their large-scale production and scalability remain serious challenges that limit clinical translation. Laboratory-scale batch preparation methods commonly used in nanomedicine development often lead to problems such as non-uniform particle size and surface properties when scaled up for industrial production. This results in poor batch-to-batch reproducibility and makes it difficult to meet GMP requirements for large-scale manufacturing. Complex nanostructures—such as those involving targeting ligand conjugation or surface stealth modifications—tend to suffer from poor uniformity, unstable surface characteristics, and impaired control over the protein corona during scale-up, ultimately reducing in vivo delivery efficiency.[223] These issues hit brain-targeted systems especially hard, often causing inconsistent ligand density and reduced BBB penetration that directly impair brain delivery performance.

Worldwide, no unified regulatory guidelines or evaluation standards specific to nanomedicines currently exist, leading to extended approval timelines.[224] Standardized protocols for critical quality attributes—such as batch-to-batch consistency and

long-term storage stability—are lacking, making it difficult to satisfy regulatory demands for quality control and stability.[225] This constitutes a key external bottleneck limiting the clinical translation of brain-targeted nanomedicines.

Despite the growing number of basic and preclinical studies on nanomedicines, very few brain-targeted formulations have actually entered clinical trials. More than 50 nanomedicines have been approved for clinical use, and over 100 are in clinical development, but brain-targeted ones remain a small fraction. The clinical translation pathway for brain-targeted nanomedicines is typically longer and more complex, with significantly extended development timelines and higher capital investment than traditional drugs.[215] In particular, brain-targeted nanodelivery systems for psychiatric disorders remain mostly at the preclinical stage, and their clinical translation lags substantially behind.

Strategies to promote the clinical translation of nanoformulations include microfluidics-based controllable scale-up,[226] quality-by-design for full-process control, mild post-processing techniques, nano-redevelopment of active molecules with proven safety (eg, curcumin,[227] nitric oxide synthase modulators[228]), exploration of novel delivery targets and disease-relevant models (eg, the gut-microbiota-immune-brain axis[229]), and the design of biodegradable, low-immunogenicity nanocarriers. The synergistic implementation of these strategies can enhance scalability, batch-to-batch consistency, and translational feasibility.

Future Perspectives

In the future, precision and personalization will become central directions for nanodelivery systems in psychiatric disorders. Clinical diagnosis will gradually shift toward biomarker-driven precision subtyping, which may reduce the high misdiagnosis rate (up to 75%) in diseases such as schizoaffective disorder,[230] providing a basis for targeted design and dosage optimization of nanocarriers. Artificial intelligence will play a key role in disease subtyping, target identification, and carrier optimization. Machine learning models based on EV proteomics can already effectively distinguish schizophrenia, bipolar disorder, and depression, supporting the development of personalized nanomedicines.[231] Meanwhile, stimuli-responsive smart nanocarriers will be deeply integrated with multimodal diagnostic platforms, enabling spatiotemporally controlled drug release in response to endogenous or exogenous signals, thereby enhancing targeting accuracy and reducing off-target effects. The synergistic integration of nanotechnology, artificial intelligence, and multimodal data will provide new opportunities for developing personalized therapeutic strategies tailored to individual pathophysiological profiles.

Conclusions

Nanodelivery systems, through their unique physicochemical properties, provide a feasible way to address clinical bottlenecks of traditional antipsychotic drugs, including delayed onset, pronounced peripheral side effects, and poor compliance, by improving drug solubility, optimizing in vivo transport, and enhancing brain delivery efficiency.

This review summarizes mainstream nanocarriers including lipid-based, polymer-based, and inorganic-based systems, each with distinct construction strategies and application advantages. Among them, lipid-based NPs and exosomes can efficiently cross the BBB due to their structural features, while targeted modification and flexible combination of various materials provide a feasible route to overcome delivery barriers. Notably, some nanomaterials possess both therapeutic and diagnostic functions. GO shows neuroprotective effects, SPIONs enable theranostic integration, and biomolecules inherent in natural carriers such as exosomes offer potential for early diagnosis and drug tracking. Alongside advances in these carrier platforms, nanotechnology has expanded beyond simple drug delivery. It broadens therapeutic dimensions for psychiatric disorders via multiple mechanisms, including regulating the brain–gut axis and attenuating neural damage by intervening in oxidative stress.

However, several critical limitations remain that hinder clinical translation: insufficient long-term biosafety data, suboptimal brain-targeting efficiency, and challenges in large-scale production and batch-to-batch consistency.

Future advances in understanding nano-bio interactions, optimizing brain-targeting strategies, and improving manufacturing and quality control are expected to overcome these barriers. Smart biodegradable carriers integrated with multifunctional therapies will represent a key direction for precision psychiatry.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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