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Revisão

Nanoparticle-Based Intranasal Delivery Systems for Brain Targeting in Depression: Mechanisms, Therapeutic Outcomes, and Translational Challenges

Sistemas de Liberação Intranasal à Base de Nanopartículas para Direcionamento ao Cérebro no Tratamento da Depressão: Mecanismos, Desfechos Terapêuticos e Desafios de Translação para a Prática Clínica

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ABSTRACT

Depression is still one of the most severe worldwide health disorders, with conventional oral antidepressant medications hampered by delayed onset, significant first-pass metabolism, low adherence, and limited brain penetration. This review critically assesses nanoparticle-based intranasal delivery options designed to address these constraints. Intranasal injection allows for direct nose-to-brain transport via the olfactory and trigeminal pathways, which bypasses the blood-brain barrier and hepatic metabolism. However, traditional intranasal formulations confront problems such as enzymatic breakdown, mucociliary clearance, and a short nasal residence period. Nanocarrier systems, which include polymeric, lipid-based, and inorganic nanoparticles, improve drug solubility, stability, mucosal retention, penetration, and controlled release. Mucoadhesive coatings like chitosan enhance residence duration and paracellular transfer.

In recent preclinical investigations, antidepressant-loaded nanoparticles have shown significant pharmacokinetic and pharmacodynamic advantages, such as higher brain bioavailability, faster start of action, and improved behavioral results. Despite these advancements, clinical translation is still limited due to safety, regulatory, manufacturing, and evaluation constraints. This review summarizes current findings, highlights significant knowledge gaps, and proposes future paths to aid in the development of therapeutically applicable nanoparticle-based intranasal antidepressants.

Keywords: Depression; Intranasal delivery; Nanoparticles; Nose-to-brain targeting; Antidepressants; Drug delivery systems

RESUMO

A depressão continua sendo um dos transtornos de saúde mais graves em todo o mundo. Os medicamentos antidepressivos convencionais administrados por via oral apresentam limitações, como início de ação tardio, metabolismo de primeira passagem significativo, baixa adesão ao tratamento e penetração limitada no cérebro. Esta revisão avalia criticamente as alternativas de liberação intranasal à base de nanopartículas desenvolvidas para superar essas limitações. A administração intranasal permite o transporte direto do nariz

para o cérebro por meio das vias olfatória e trigeminal, contornando a barreira hematoencefálica e o metabolismo hepático. Entretanto, as formulações intranasais tradicionais enfrentam problemas como degradação enzimática, depuração mucociliar e curto tempo de permanência na cavidade nasal. Os sistemas de nanocarreadores, que incluem nanopartículas poliméricas, lipídicas e inorgânicas, melhoram a solubilidade, a estabilidade, a retenção na mucosa, a penetração e a liberação controlada dos fármacos. Revestimentos mucoadesivos, como os à base de quitosana, aumentam o tempo de permanência e a transferência paracelular. Em estudos pré-clínicos recentes, nanopartículas contendo antidepressivos demonstraram vantagens farmacocinéticas e farmacodinâmicas significativas, como maior biodisponibilidade cerebral, início de ação mais rápido e melhora dos resultados comportamentais. Apesar desses avanços, a translação para a prática clínica ainda é limitada por questões relacionadas à segurança, à regulamentação, à fabricação e às limitações dos métodos de avaliação. Esta revisão sintetiza os achados atuais, destaca lacunas importantes no conhecimento e propõe perspectivas futuras para auxiliar no desenvolvimento de antidepressivos intranasais à base de nanopartículas com aplicabilidade terapêutica.

Palavras-chave: Depressão; Administração intranasal; Nanopartículas; Direcionamento do nariz para o cérebro; Antidepressivos; Sistemas de liberação de fármacos.

1. INTRODUCTION

Depression significantly reduces quality of life, productivity, and social functioning and is a major contributor to the burden of disease and disability worldwide [1-2]. Despite the availability of various pharmacological classes, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and atypical drugs, treatment outcomes are nevertheless unsatisfactory for a considerable minority of patients[1-2]. Conventional oral medication has enduring problems, including delayed beginning of action, variable bioavailability, systemic side effects, low adherence, and limited central nervous system (CNS) drug exposure [3-6]. A significant pharmacokinetic restriction of oral antidepressants is considerable first-pass metabolism and restricted transport across the blood-brain barrier (BBB), resulting in low brain drug concentrations compared to systemic exposure[3-6]. Higher dosages are therefore frequently needed to achieve therapeutic efficacy, raising the possibility of side effects and further jeopardizing adherence[3-6]. These drawbacks highlight the need for alternate delivery methods that can improve brain targeting while reducing systemic burden.

Intranasal administration has emerged as a viable non-invasive approach for direct CNS medication delivery, enabling bypass of the BBB through the olfactory and trigeminal neuronal pathways [3–6,8]. This method promotes rapid brain absorption and avoids hepatic metabolism, delivering possible advantages such as faster beginning of action and enhanced therapeutic index[3,5,6]. However, physiological constraints such mucociliary clearance, enzymatic degradation, limited residence duration, and reduced absorption surface area limit the bioavailability and therapeutic consistency of typical intranasal formulations [7,8,21].

Drug delivery methods based on nanotechnology offer creative answers to these problems. Inorganic, lipid-based, and polymeric nanoparticles can increase drug solubility, shield labile molecules from enzymatic breakdown, increase epithelial penetration, extend nasal residence, and permit controlled release [9–12,14]. Surface modification with mucoadhesive polymers, such as chitosan, improves retention and paracellular transport by transitory manipulation of tight junctions [13,14,22]. A significant amount of preclinical research over the last 10 years has shown that intranasal administration boosted by nanoparticles has the potential to improve the pharmacokinetics and pharmacodynamics of antidepressants [11,15–18].

The present review aims to critically evaluate the mechanisms, formulation strategies, therapeutic outcomes, and translational challenges associated with nanoparticle-based intranasal delivery systems for depression. By synthesizing current evidence and identifying key knowledge gaps, this review seeks to inform future research directions and support the clinical translation of nose-to-brain nanomedicine for psychiatric disorders.

2. LITERATURE SEARCH METHODOLOGY

A comprehensive literature search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Articles published between 2013 and 2025 were considered. Search terms included combinations of "intranasal delivery," "nose-to-brain," "nanoparticles," "antidepressants," "depression," "CNS drug delivery," and "mucoadhesive systems." Inclusion criteria comprised original research articles and high-quality review papers focusing on nanoparticle-based intranasal delivery of antidepressants or CNS-active agents with direct relevance to depression. Exclusion criteria included non-nasal delivery routes, non-nanoparticle formulations, studies unrelated to CNS targeting, and non-English publications. Reference lists of selected articles were manually screened to identify additional relevant studies

3. ANATOMICAL AND PHYSIOLOGICAL BASIS OF NOSE-TO-BRAIN DRUG TRANSPORT

The nasal cavity serves as a unique anatomical contact between the external environment and the central nervous system. The olfactory and trigeminal nerves are the primary neural routes that carry drugs from the nasal cavity to the brain [3–6,8]. The olfactory area, which is situated in the upper posterior nasal cavity, allows drugs to flow through the BBB since it has direct access to the olfactory bulb [3,5,6]. The trigeminal nerve helps carry drugs to the brainstem and other parts of the central nervous system (CNS) and innervates the respiratory and olfactory areas [3,5,6].In addition to neuronal routes, extraneuronal processes such as paracellular diffusion and transcellular transport across the nasal epithelium contribute to drug absorption [7,8,21]. However, a number of physiological obstacles prevent effective drug administration, such as nasal peptidases' enzymatic breakdown, quick mucociliary clearance, the nasal epithelium's low permeability, and limited dosage volume [7,8,21]. These obstacles compromise the regularity of treatment by causing a short residence period and inconsistent drug absorption. Efflux transporters and metabolic enzymes found in the nasal mucosa further limit medication entry into the CNS [7,21]. These physiological limits need the development of new delivery systems capable of improving retention, stability, permeation, and targeting efficiency [9–12,14].

4. LIMITATIONS OF CONVENTIONAL INTRANASAL ANTIDEPRESSANT DELIVERY

Conventional formulations including aqueous solutions, suspensions, and simple gels are still less than ideal for CNS drug targeting, despite the potential benefits of intranasal administration [7,8,21]. Limited drug absorption results from rapid mucociliary clearance, which shortens the formulation's contact time with the absorptive epithelium [7, 8]. The stability of many antidepressants, especially peptides and labile compounds, is further compromised by enzymatic breakdown in the nasal cavity [7,21].

Additionally, the nasal mucosa has low permeability to hydrophilic and high-molecular-weight substances, which limits passive diffusion [7,8,21]. The minimal permitted dose volume (25-200 µL each nostril) limits drug loading and therapeutic dosing [7, 8]. Variability in nasal physiology, pathology, and administration technique all contribute to uneven medication distribution and treatment effects [3, 6, 21].

These limitations underscore the importance of innovative formulation techniques that can improve stability, retention, permeation, and targeting efficiency while ensuring mucosal safety and patient acceptance [9-12,14].

5. NANOTECHNOLOGY-BASED STRATEGIES FOR INTRANASAL ANTIDEPRESSANT DELIVERY

Drug delivery techniques based on nanoparticles have been thoroughly studied as ways to get around the drawbacks of traditional intranasal formulations. These methods improve epithelial penetration, increase nasal residence time, prevent enzymatic degradation, increase drug solubility, and allow for regulated release [9–12,14]. Polymeric nanoparticles, lipid-based systems, nanoemulsions, and mucoadhesive surface-modified carriers are

important nanocarrier classes investigated for intranasal antidepressant delivery [11,12,15–18].

5.1 POLYMERIC NANOPARTICLES

Polymeric nanoparticles, notably those derived from poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and related biopolymers, are frequently employed due to their biodegradability, biocompatibility, and tunable release patterns [9-12,14]. Chitosan-coated systems are of special interest because of their mucoadhesive qualities and capacity to temporarily open tight junctions, boosting paracellular transport[13,14,22]. Antidepressant-loaded polymeric nanoparticles have been shown in numerous studies to significantly increase brain uptake after intranasal administration. For example, paroxetine-loaded PLGA–chitosan nanoparticles showed about four times higher brain concentrations than conventional formulations, which were attributed to prolonged nasal residence and enhanced epithelial permeation [11]. Similarly, venlafaxine-loaded alginate nanoparticles produced significant increases in brain area under the concentration–time curve (AUC) and improved behaviour in rodent models [16]. Additionally, these systems have controlled release characteristics that allow for prolonged drug delivery and may lessen the frequency of doses [9–12]. But polymeric nanoparticles can be sensitive to formulation characteristics, have batch-to-batch variability, and be difficult to scale up, therefore strong production and quality control methods are required [19,20].

5.2 LIPID-BASED NANOCARRIERS

Solid lipid nanoparticles (SLNs), liposomes, lipid nanocapsules, and nanostructured lipid carriers (NLCs) are examples of lipid-based nanocarriers that provide benefits such increased membrane permeability, greater physical stability, and a high drug-loading capacity [10–12]. Their lipidic composition makes it easier for them to interact with biological membranes, which encourages transcellular transport and may improve neuronal uptake[10–12]. Pharmacokinetic and pharmacodynamic results have consistently improved when antidepressants are delivered intranasally via lipid-based methods. When compared to oral or traditional intranasal formulations, SLN and NLC formulations of sertraline, duloxetine, fluoxetine, mirtazapine, and agomelatine have demonstrated improved behavioural efficacy, accelerated start of action, and greater brain bioavailability [13,15,17,18]. High entrapment efficiency and acceptable stability characteristics have also been demonstrated by lipid nanocapsules, confirming their applicability for CNS targeting [13].Lipid-based systems may encounter issues with polymorphic transitions, long-term stability, and drug ejection during storage despite these benefits; these issues need to be resolved by careful stability testing and formulation design optimization [10–12,19].

5.3 NANOEMULSIONS AND NANOSUSPENSIONS

Nanoemulsions and nanosuspensions provide easy and scalable formulation platforms for intranasal administration of antidepressants that are poorly water soluble [12,18]. These methods improve solubility, increase mucosal contact, and speed up drug absorption [12,18]. Several nanoemulsion-based formulations of paroxetine, fluoxetine, and other antidepressants have showed enhanced brain targeting and faster pharmacological response after intranasal administration [17,18].While these systems are easy to manufacture and have a large drug-loading capacity, they lack the controlled release and long-term retention that polymeric and lipid nanoparticles provide [12]. As a result, nanoemulsions and nanosuspensions may need additional mucoadhesive or surface-modifying techniques to obtain lasting therapeutic results [12,14].

5.4 MUCOADHESIVE AND SURFACE-MODIFIED NANOCARRIERS

Surface modification of nanoparticles with mucoadhesive polymers such chitosan, carbopol, hyaluronic acid, and lectins has emerged as an important method for increasing nasal residency length and epithelial contact [13,14,22]. Mucoadhesive coatings prolong contact with the nasal mucosa, limit mucociliary clearance, and improve paracellular transport via transitory modification of tight junctions [13,14,22].Chitosan-coated nanoparticles have consistently shown better mucoadhesion, penetration, and brain targeting than uncoated systems [11-14,22]. Ligand-functionalized nanoparticles, such as those coated with transferrin, lactoferrin, or cell-penetrating peptides, have also been investigated for improving receptor-mediated uptake

and neuronal targeting [24]. While these tactics offer promise improvements in targeting efficiency, they entail additional formulation complexity, regulatory scrutiny, and safety concerns that must be carefully addressed [19,20,24].

6. PHARMACOKINETIC AND PHARMACODYNAMIC OUTCOMES

Pharmacokinetic characteristics, such as greater brain AUC, higher peak brain concentrations (C_max), decreased systemic exposure, and shorter time to peak concentration (T_max), have been shown to significantly improve with nanoparticle--enhanced intranasal delivery [11,13,15–18]. In preclinical models of depression, these pharmacokinetic improvements result in better pharmacodynamic outcomes, as demonstrated by increased behavioral efficacy [15–18,25]. Antidepressant-loaded nanoparticles have proven to function better than oral and traditional intranasal formulations in a number of investigations. While venlafaxine-loaded alginate nanoparticles resulted in a threefold rise in brain AUC [16], paroxetine-loaded PLGA–chitosan nanoparticles obtained around fourfold higher brain uptake [11]. In behavioral tests like the forced swim test, tail suspension test, and sucrose preference test, lipid-based systems for sertraline, duloxetine, fluoxetine, mirtazapine, and escitalopram have continuously demonstrated high entrapment efficiency, improved permeation, and quicker onset of antidepressant--like effects [13,15,17,18].However, direct comparison among research remains difficult due to differences in animal models, dosing regimens, formulation compositions, and outcome assessments [3,6,25]. Standardizing experimental techniques and reporting practices is required to promote cross-study comparison and translational interpretation [6,25].

7. CLINICAL TRANSLATION AND REGULATORY CONSIDERATIONS

Despite promising preclinical results, the practical application of nanoparticle-based intranasal antidepressant administration is restricted. The United States has not approved any nanoparticle-based intranasal antidepressant formulations. Too far, the Food and Drug Administration or the European Medicines Agency has highlighted the translational gap between laboratory research and clinical use [3,6,19,20].Nasal epithelium irritation, mucociliary dysfunction, immunogenicity, neurotoxicity, and possible accumulation inside brain tissues are some of the safety concerns related with prolonged intranasal nanoparticle treatment [7,8,19,20]. Long-term toxicity data are sparse, particularly for repeated exposure, bioaccumulation, and potential effects on olfactory and trigeminal nerve function [7,8,19,20]. Regulatory agencies emphasize the importance of thorough safety evaluation, which includes immunotoxicity, neurotoxicity, biodistribution, metabolism, and clearance studies[9,19,20]. Additional translational issues include complex physicochemical characterisation, batch-to-batch variability, long-term stability, sterilization, and manufacturing process scaling [9,19,20]. Device--formulation compatibility, patient acceptability, dosage precision, and administration strategy all have an impact on clinical feasibility [3,6,21]. Furthermore, clinical assessment of nose-to-brain transport remains difficult due to limitations in non--invasive imaging and established biomarkers for direct CNS drug quantification in humans [6,26].

8. FUTURE PERSPECTIVES

Future research should focus the creation of therapeutically applicable nanoparticle systems with optimal safety profiles, scalable production techniques, and strong regulatory compliance [9,19,20]. Advanced techniques, such as ligand-targeted nanoparticles, stimuli-responsive systems, and multifunctional nanocarriers, can improve site-specific delivery, reduce off-target exposure, and improve therapeutic effects [23,24].

Integration of imaging-based pharmacokinetic assessment, such as positron emission tomography and magnetic resonance imaging-guided tracking, will be critical for confirming nose-to-brain transport and therapeutic distribution in people [26]. Harmonization of regulatory requirements, uniform characterisation techniques, and established pharmacodynamic endpoints will further simplify clinical translation [6,19,20].

To promote real-world clinical success, patient-centric formulation design must include aspects such as device compatibility, dosage convenience,

formulation acceptance, and adherence [3,6,21]. Collaboration among formulation scientists, physicians, regulatory agencies, and industry stakeholders will be important in moving nanoparticle-based intranasal antidepressant medicines from bench to bedside. [9,19,20].

9. CONCLUSION

Nanoparticle-based intranasal administration is a highly promising technique for addressing the pharmacokinetic and therapeutic limitations of traditional antidepressant treatment. Nanocarriers have the potential to improve drug stability, nasal residence length, epithelial permeation, and brain targeting efficiency, resulting in a speedier beginning of action, improved efficacy, and less systemic side effects [9-12, 14-18]. Although extensive preclinical evidence supports the viability and therapeutic benefit of this method, significant obstacles remain in terms of safety, regulatory approval, manufacturing scalability, and clinical evaluation [3,6,19,20]. Addressing these issues through standardized procedures, rigorous safety assessments, and translationally appropriate trial designs is critical to achieving nose-to-brain nanomedicine's clinical potential in depression treatment.

DATA AVAILABILITY STATEMENT:

All data supporting the finding of this study are included within the article and its referenced sources.

Author Contributions:
Conceptualization: V.J.B
Literature Review: V.J.B
Writing: V.J.B
Draft: C.P.J
Review and Editing: V.J.B
Supervision: C.P.J

Table 1. Representative nanoparticle-based intranasal antidepressant formulations.

Drug	Nanocarrier System	Key Characteristics	In Vivo Outcome	Reference
Paroxetine	PLGA–chitosan nanoparticles	Mucoadhesive, controlled release	~4-fold increase in brain uptake; enhanced behavioral efficacy	[11]
Escitalopram	Chitosan nanoparticles	Tight junction modulation, prolonged retention	Increased brain bioavailability and antidepressant-like effects	[12]
Venlafaxine	Alginate nanoparticles	Sustained release, enhanced permeation	~3-fold increase in brain AUC; improved pharmacodynamics	[16]
Mirtazapine	Lipid nanocapsules	High drug loading, membrane affinity	Higher brain concentration and faster onset of action	[13]
Duloxetine	PLGA nanoparticles	Stable nanosystem, controlled release	Enhanced brain targeting and behavioral response	[15]
Agomelatine	Solid lipid nanoparticles	Improved stability, high entrapment efficiency	Increased brain targeting efficiency and PK performance	[17]
Paroxetine	Solid lipid nanoparticles	Lipid-based permeation enhancement	Improved brain distribution and antidepressant activity	[18]

Table 2. Advantages and limitations of major nanocarrier systems for intranasal antidepressant delivery

Nanocarrier Type	Advantages	Limitations
Polymeric nanoparticles	Controlled release, tunable properties, biodegradability	Scale-up complexity, batch variability
Lipid-based nanoparticles (SLN/NLC)	High drug loading, membrane affinity, good stability	Risk of drug expulsion, polymorphic transitions
Nanoemulsions	Simple formulation, high solubility enhancement	Limited sustained release, rapid clearance
Mucoadhesive-coated systems	Prolonged residence time, enhanced permeation	Possible mucosal irritation, regulatory scrutiny

Table 3. Key translational and regulatory challenges in nanoparticle-based intranasal antidepressant delivery

Category	Challenge
Safety	Nasal toxicity, neurotoxicity, immunogenicity, accumulation risk
Regulatory	Lack of standardized evaluation frameworks for nanomedicines
Manufacturing	Scale-up, reproducibility, sterilization, stability
Clinical Evaluation	Limited non-invasive tools to quantify brain drug delivery
Patient Use	Device compatibility, dosing precision, adherence

REFERENCES

1. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649–59.
2. Brown S, Rittenbach K, Cheung S, McKean G, MacMaster FP, Clement F. Current and common definitions of treatment-resistant depression: Findings from a systematic review and qualitative interviews. Can J Psychiatry. 2019;64(6):380–7.
3. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release. 2018; 281:139–77.
4. Kumar NN, Gautam M, Lochhead JJ, Wolak DJ, Thorne RG. Relative vascular permeability and vascular surface area product of the blood–brain barrier and blood–cerebrospinal fluid barrier in the rat brain. J Cereb Blood Flow Metab. 2016;36(9):1522–35.
5. Han L, Zhang Y, Chen Y, Shu Y, Huang Z, Chen X. Nose-to-brain drug delivery systems for central nervous system diseases: Recent advances and challenges. Drug Deliv. 2023;30(1):222–45.
6. Jeong SH, Kim DW, Park JH, Lee S, Kim JH. Intranasal delivery systems for CNS therapeutics: Physiology, formulation strategies, and regulatory perspectives. Pharmaceutics. 2022;14(7):1423.
7. Oliveira H, Pires LR, Fernández-Gutiérrez M, Sanchez A, Alonso MJ. Nose-to-brain delivery of therapeutic peptides and proteins. J Control Release. 2016; 224:93–107.
8. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci. 2018; 195:44–52.
9. EMA. Reflection paper on nanotechnology-based medicinal products for human use. London: European Medicines Agency; 2018.
10. FDA. Guidance for industry: Considering whether an FDA-regulated product involves the application of nanotechnology. Silver Spring, MD: U.S. Food and Drug Administration; 2014.
11. Sharma G, Kamboj S, Thakur K, Negi P, Raza K. Intranasal delivery of paroxetine-loaded chitosan-coated PLGA nanoparticles: Pharmacokinetic and behavioral evaluation. Int J Pharm. 2025; 629:122449.
12. Jain K, Kesharwani P, Gupta U, Jain NK. A review of drug delivery systems for brain targeting: Recent advances. Drug Deliv Transl Res. 2019;9(2):243–67.
13. Ibrahim MM, Abd El-Halim SM, Ahmed AA. Lipid nanocapsules for intranasal delivery of mirtazapine: In vivo brain targeting and antidepressant activity. Colloids Surf B Biointerfaces. 2024; 224:113237.
14. Carvalho FC, Bruschi ML, Evangelista RC, Gremião MP. Mucoadhesive drug delivery systems. Braz J Pharm Sci. 2010;46(1):1–17.
15. Salem HF, Kharshoum RM, Abdelrahim MEA. Intranasal delivery of duloxetine-loaded PLGA nanoparticles for enhanced brain targeting. Drug Dev Ind Pharm. 2023;49(3):402–13.
16. Cayero-Otero MD, Morales M, Rodríguez F, García-González CA. Intranasal venlafaxine-loaded polymeric nanoparticles for enhanced brain delivery. Eur J Pharm Sci. 2025; 186:106465.
17. Fatouh AM, Elshafeey AH, Abdelbary G. Intranasal agomelatine solid lipid nanoparticles: Formulation, in vivo pharmacokinetics and brain targeting efficiency. Int J Pharm. 2017;529(1–2):443–51.

18. Pandey A, Jain SK. Solid lipid nanoparticles of paroxetine: Formulation and brain targeting by intranasal delivery. Drug Deliv. 2015;22(8):1155–65.

19. EMA. Reflection paper on nanotechnology-based medicinal products for human use. London: European Medicines Agency; 2018.

20. FDA. Guidance for industry: Considering whether an FDA-regulated product involves the application of nanotechnology. Silver Spring, MD: U.S. Food and Drug Administration; 2014.

21. Illum L. Nasal drug delivery—Possibilities, problems and solutions. J Control Release. 2003;87(1–3):187–98.

22. Maher S, Mrsny RJ. Engineering the mucosal interface for the treatment of central nervous system disorders. J Control Release. 2023; 353:205–18.

23. Liu Y, Jiang S, Li Y, Wu M, Wang H. Ligand-modified nanoparticles for nose-to-brain drug delivery. Acta Pharm Sin B. 2024;14(1):85–104.

24. Sosnik A, Carcaboso AM. Nanomedicines for the delivery of therapeutic oligonucleotides. Mol Pharm. 2014;11(11):3780–801.

25. Xu Q, Huang Y, Wang Z, Wang X, Jiang Y. Behavioral evaluation of antidepressant efficacy in animal models. Pharmacol Biochem Behav. 2020; 193:172918.

26. Han X, Chen J, Zhang Q, Li L. Imaging-based evaluation of nose-to-brain drug delivery. Adv Drug Deliv Rev. 2023; 197:114799.