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Review Article

Revolutionizing Psychiatric Care: Nanotechnology-Driven Nose-To-Brain Therapy

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ABSTRACT

Anxiety and Depression are widespread mental health conditions that have a major influence on people's quality of life and overall health worldwide. The effectiveness of traditional pharmacological treatments is frequently limited by issues such systemic side effects, delayed therapeutic onset, and poor blood-brain barrier (BBB) penetration. One innovative way to overcome these constraints is through nanotechnology, especially with nose-to-brain drug delivery devices. Therapeutics can be delivered directly and quickly to the Central Nervous System (CNS) via the nasal route, which avoids the blood-brain barrier. Solid lipid nanoparticles (SLNs), polymeric nanoparticles, liposomes, and nanoemulsions are examples of nanocarriers that have shown great promise in improving medication targeting, bioavailability, and controlled release. This method lowers systemic exposure, increases patient compliance, and maximizes therapeutic results. This review examines the developments in nose-to-brain therapy for depression and anxiety that are powered by nanotechnology. Important nanocarrier systems, their modes of action, therapeutic uses, and the difficulties in clinical translation are highlighted. The revolutionary potential of these discoveries to alter psychiatric care and give those afflicted with these crippling conditions new hope is emphasized.

INTRODUCTION

Mental illnesses continued to rank among the top ten worldwide health burdens, rising 48.1% from 654 million cases in 1990 to 970 million cases in 2019. The World Health Organization (WHO) estimates that one out of eight individuals have a mental illness, with depression affecting about 280 million people, including 23 million children and adolescents [1]. The importance of mental health in society cannot be overstated, and more funding is required to support both the discovery of novel treatments and the easier access to current, successful treatments. One of the main causes of

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disability in the world, depression also has a role in the emergence of other illnesses, such as cardiovascular, metabolic, and neuropsychiatric disorders. It is linked to a lower quality of life and is typified by a lack of interest in daily activities, melancholy, anger, exhaustion, guilt feelings, low self-esteem, sleep issues, and suicide thoughts, among other things. There are two primary types of depression: major depression, which has more severe symptoms and a higher emotional weight, and minor depression, which has less symptoms and permits normal daily functioning. A monoaminergic transmission disorder, or a disruption in the brain's transmission of serotonin, norepinephrine, and dopamine, is the basis of the most widely accepted theory regarding the pathophysiology of depression. This is caused by the complex interaction of multiple social (such as a traumatic life), psychological (such as personality), and biological (such as a genetic predisposition) factors [2-8].

Due to the lack of pancreatic and stomach enzymatic activity and interference from gastrointestinal contents, the nasal mucosa is more permeable to substances than the gastrointestinal system. Only topical administrations of medications meant for local effects were covered by the earliest known historical use of nasal drug delivery. Nasal drug delivery has attracted a lot of interest lately since it is a practical, promising, and dependable way to deliver medications to the body, particularly those that cannot be taken orally and need to be injected. High overall blood flow, a porous endothelium membrane, a big surface area, and easy accessibility are all provided by this pathway. In order to have both local and systemic effects, its application has recently expanded to target numerous other body parts. Additionally, nasal drug delivery has a specific role in traditional medical systems like Ayurvedic Indian medicine, which refers to it as "Nasya karma" and is a widely accepted kind of treatment [9-12].

The human brain is among the most intricate and important organs, it controls the majority of bodily processes and receives messages from sensory organs. It regulates hormone secretion, memory encoding, voluntary and involuntary motions, and several other organ processes [13]. The brain is safeguarded both internally and outside because of its vital significance in the human body. Cerebrospinal fluid (CSF), the CSF-blood barrier, and the blood-brain barrier (BBB) provide internal protection, while the skull's many membrane layers guard against external harm. These barriers protect against infections, endotoxins, physical harm, and other adverse effects while also helping to maintain the brain's balance [14-18]. The blood-brain barrier (BBB) and cerebrospinal fluid (CSF) protect the central nervous system (CNS) from external damage and preserve its integrity and homeostasis while keeping it isolated from the systemic circulation. An essential component of brain function is the blood-brain barrier (BBB), which keeps external blood components out of the extracellular fluid of the brain. Its existence was originally verified by Paul Ehrlich in 1885, and Edwin Goldman followed suit in 1913. Animal models demonstrated the BBB's role in preventing dyes from moving from blood to the central nervous system. Further research has improved our understanding of the BBB's physiological and anatomical characteristics and its role in drug entry. Intranasal (IN) administration is a potentially effective way to administer medications to the brain, offering a minimally invasive and rapid route compared to traditional parenteral and oral routes. The nasal cavity has unique anatomical characteristics, allowing for rapid action and avoiding hepatic first pass-effect. The IN route has been extensively studied for topical and systemic treatments, with a surface area of around 160 cm^2 and a high-density microvasculature responsible for drug absorption and distribution. However, nose physiology

presents challenges, such as limited formulation volume, mucociliary clearance, mucus layer presence, and local enzymes. Drug delivery methods based on nanoparticles have demonstrated the capacity to improve drug accumulation in the central nervous system by increasing olfactory area penetration. This article critically reviews recent progress in developing nanoparticles (NP) for IN drug delivery, focusing on their nanocarrier nature, including polymer, lipid, inorganic NP, and drug nanocrystals [19-21].

PATHWAYS OF NOSE-TO-BRAIN TRANSPORT

1. ANATOMY OF THE NASAL CAVITY:

The human nose consists of four anatomical components: the nasal cavity, external nose, paranasal sinuses, and nasopharynx. It comprises five areas: radix, dorsum, apex, ala, and nares, partially composed of nasal bones and cartilage. The nasal cavity is responsible for dust adsorption, humidification, and warming of inspired air. There are mucous membranes lining it and supported by bone and cartilage. The nasal septum splits the nasal cavity into left and right cavities. The nasal cavity is about 12 cm long and the volume of each nasal cavity is 13ml with a total area of 150-160 cm^2 [22-23]. Both the external nose and the nasal cavity, which are essential for respiratory function, are parts of the intricate nasal architecture. The visible aperture for inhaled air is the external nose, which is composed of bone and cartilage. Upon entering the nasal cavity, which is partitioned by the nasal septum, it serves as the major conduit for respiratory function. Particulate debris and foreign particles are efficiently removed from inhaled air by the specialized cilia of the respiratory epithelium, which lining the nasal passages. These cilia act as microscopic brooms. At the same time, the mucosal membrane's blood vessels help with air conditioning by warming and hydrating the air that is inhaled [24-26].

The nasal cavity can be separated into vestibular, respiratory, and olfactory areas based on its structure and function. With a tiny surface area and minimal absorptive capacity, the vestibular region is a modest expansion that occurs inside the nostrils and before the main nasal cavity. Pharyngeal cells, cilia cells, intermediate cells, and basal cells are among the many epithelial cells found in the respiratory region. Numerous nasal glands and microhairs cover the mucosal surface cells, which significantly improves the absorption of drugs. As a result, medications enter the systemic circulation mostly through the respiratory system. The olfactory area, which is composed of olfactory sensory neurons, basal cells, and sustentacular cells, is mostly linked to CNS administration. The axons, dendrites, and cell body make up the three components of OSNs, which are specialized bipolar neurons situated in the space between supporting cells. The central processes of olfactory cells stretch through the epithelium's basal layer and then come together to create olfactory filament nerve bundles. The nerve sheath is formed by olfactory ensheathing cells (OEC) and olfactory nerve fibroblasts encircling the olfactory filament. The ethmoid bone's cribriform plate allows the olfactory filament to enter the brain, where it ends in the olfactory bulb. As a result, this area has a direct connection to the nasal delivery of medication to the brain [27-30].

2. NOSE-TO-BRAIN TRANSPORT PATHWAYS:

Drug delivery through the olfactory mucosa has been studied to administer medicinal drugs to the brain to treat CNS diseases. As previously described, it has the significant advantage of bypassing the blood-brain barrier and reducing systemic exposure. Major potential routes for nose-to-brain delivery have been suggested by a number of recent studies. These include indirect drug delivery via the lymphatic and vasculature systems, which cause the brain to cross the blood-

brain barrier, and direct drug delivery to the brain via neuronal pathways such as the Olfactory Nerve Pathway and Trigeminal Nerve Pathway. The following pathways are typically used to overcome the barriers.

2.1. OLFACTORY NERVE PATHWAY:

The olfactory nerve pathway is a key route for drug targeting the brain through intranasal delivery. It is located at the upper portion of the nasal cavity and contains olfactory receptor neurons (ORNs) and supporting cells. ORNs convey sensory information from the peripheral surrounds to the central nervous system (CNS). The olfactory region includes bowman's glands, axons, lymphatic vessels, blood vessels, and connective tissue. Whereas the axons of olfactory neurons extend centrally in the cribriform plate of ethmoid bone, the dendrites extend in the mucous tissue. The stem of the olfactory neuron passes through the subarachnoid space, extending towards various brain regions. Drug transport across the olfactory epithelium can generally include three distinct pathways: (1) the transcellular (particularly between sustentacular cells) pathway, which is primarily in charge of transporting lipophilic medicines and typically involves endocytosis or passive diffusion; (2) the paracellular (between sustentacular cells) pathway. The pace at which hydrophilic medicines are transported via this route is determined by the drug's molecular weight. This pathway allows for the good bioavailability of drugs with molecular weights up to 1000 Da or more (with an absorption enhancer); (3) the olfactory nerve pathway, where the drug's absorption into the neuronal cell and subsequent intracellular axonal transit to the olfactory bulb are influenced by endocytosis.

The olfactory nerve, originating from the nasal mucosa, is a sensory nerve that transmits information about odors to the brain. It is the shortest and first cranial nerve cranial nerve and is the unique visceral afferent nerve that conveys information relating to smell. To travel from the nasal cavity to the cerebrospinal fluid (CSF) or brain parenchyma, a drug needs to pass through the arachnoid membrane that encloses the subarachnoid space as well as the nasal olfactory epithelium. Odorants enter the nose and disintegrate into the mucous membrane, triggering a signaling cascade that transforms chemical signals into electrical signals. One can categorize the olfactory route into three pathways: transcellular, paracellular, and olfactory nerve pathways. Drugs are taken up into neuronal cells through endocytosis or pinocytosis mechanisms and transported via intracellular transfer of axons to the olfactory bulb. The nose-to-brain route has high potential for treating CNS pathologies, but it has limitations due to low drug doses due to low permeability of molecules through the mucosa, mucociliary clearance, and enzymatic degradation [31-32].

2.2. TRIGEMINAL NERVE PATHWAY:

The trigeminal nerve, the fifth cranial nerve and the thickest on the face, has three large branches. These branches, including the mandibular, maxillary, and ophthalmic nerves, extend into the olfactory and respiratory regions of the nasal cavity [33]. The opposite end ends in the brain's spinal nucleus of the trigeminal nerve after entering the central nervous system (CNS) at the pontine site [34]. Substances can be carried into the brain through the intra-axonal pathway of neurons, offering a new perspective on drug delivery [35].

The trigeminal nasal route is an essential conduit that links the nasal passages to the central nervous system (CNS). The trigeminal nerve innervates the respiratory and olfactory epithelium of the nasal passages and enters the CNS through the pons. The olfactory bulbs are also where a tiny percentage of trigeminal nerves terminate. The capacity of the trigeminal nerve to enter the brain

from the nasal passage's respiratory epithelium at two distinct sites —i) Through the lacerated foramen in front of the pons and ii) through the cribriform plate close to the olfactory bulb of the nose —makes it unique. It establishes entry sites into the rostral and caudal regions of the brain following intranasal administration [36]. Through its ophthalmic division (V1), maxillary division (V2), or mandibular division (V3), the trigeminal nerve transmits sensory data from the nasal cavity, oral cavity, eyelids, and cornea to the central nervous system. While the latter have both motor and sensory functions, the former two only have sensory functions. Since neurons from the ophthalmic and maxillary several trigeminal nerves branches travel straight through the nasal mucosa, these branches are crucial for medication transport from the nose to the brain [37].

NANOFORMULATIONS FOR NOSE-TO-BRAIN DRUG DELIVERY OF NEUROPSYCHIATRIC DISORDER:

Nasal delivery methods based on nanotechnology have drawn attention as a means of addressing issues such as excessive dosages, undesirable side effects, rapid metabolism and removal, restricted brain exposure, and low drug bioavailability. Numerous methods, including delivery systems, liposomes, polymeric and solid lipid nanoparticles (SLNs), solid lipid carriers, liquid crystals (LCs), microemulsions, and in-situ gels, have been developed to get across the blood-brain barrier. Particles of matter with a dimension of one to a thousand nanometers (nm) are called nanoparticles [38-39]. Innovative drug formulations and devices must be developed simultaneously to improve drug delivery efficacy via the respiratory system. One particularly promising strategy for getting over obstacles to medication delivery is nanoformulation. Nanocarriers are crucial for increasing the efficacy of drugs and are promising formulations, making them important subjects in clinical and preclinical research settings. Lipid NFs have become increasingly popular for delivering medications to the brain. Their nanosize allows for effective medication transport across the blood-brain barrier by avoiding biological barriers. Moreover, they offer various advantages, including controlled and precise drug delivery, minimal unfavorable drug reactions, extended shelf life, increased drug absorption, and decreased drug removal to obtain an ideal therapeutic drug level in the brain [40-41].

NANOPARTICLES:

Drug delivery by nanoparticles from the nose to the brain shows promise and provides a versatile platform to get beyond barriers. These tiny particles are usually between one and one hundred nanometers in size, improve drug stability, regulate release, and deliver them specifically to specific brain parts. They ensure constant and regulated administration by offering regulation of medication release rates. Their ability to interact with living tissues and lack of toxicity make them safe, reducing negative impacts on the nasal lining and brain. Formulations like liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLN), and dendrimers (fig. 1) offer customized drug administration approaches. Nanoparticles have a lot of potential for delivering drugs from the nose to the brain, and they are always being developed to increase their precise and efficient delivery for neurological conditions [42-44].

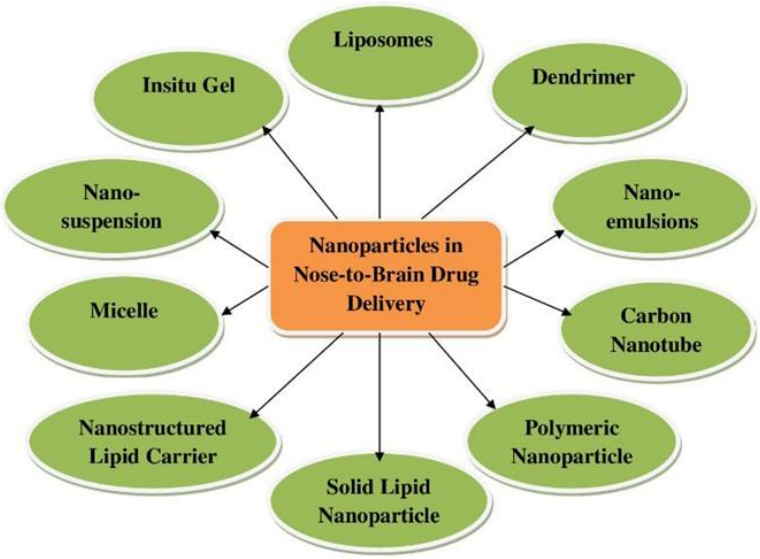

Fig. 1. Nanoparticles in Nose-to-Brain Drug Delivery

1. LIPOSOMES:

Liposomes are vesicles that range in size from 20 to 1000 nm and are made up of one or more phospholipid bilayers encircling an aqueous core. The hydrophilic (in the core) or hydrophobic (in the phospholipid bilayers) medications that will be delivered to the site of action can be incorporated thanks to their composition. However, they have several drawbacks, such as limited encapsulation effectiveness, irreproducibility between batches, system instability, the unintended release of the encapsulated material, and trouble managing liposome size [45-46].

Liposomes, which are frequently composed of phospholipid bilayers and other lipids such as cholesterol or phosphatidylcholine, are commonly utilized lipid-based nanoparticles for drug delivery systems. They can combine hydrophilic or hydrophobic active ingredients to form multiplexes with negatively charged nucleic acids. Numerous CNS illnesses have been treated with liposomes in N2B delivery experiments. Using 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG, they created a donepezil-loaded liposome to assess the pharmacokinetics in the brain and plasma following intranasal delivery. Compared to free fentanyl IN, the liposomes had a stronger analgesic effect and decreased plasma drug exposure. Fentanyl is retained in the nasal and olfactory epithelium longer when the RGD peptide liposomes attach to integrin proteins on the nasal epithelium. Drug concentration in the brain may have increased with intranasal liposomal administration, whereas systemic exposure may have reduced [47-57].

2. NANOEMULSIONS

Nanoemulsions are combinations of isotropic oil, surfactant, cosurfactant, and drug, with colloidal sizes ranging from 50-100 nm. They are transparent, translucent, and stable against sedimentation or creaming. These carriers are of interest in chemical, cosmetic, pharmaceutical, and biopharmaceutical fields [58-60]. Nanoemulsions consist of two immiscible liquids (oil and water) that combine to create a single phase when an emulsifying agent is added. They

enable rapid drug absorption into the brain and are biodegradable. However, they have drawbacks like high melting point difficulty, the need for surfactants, and high production costs [61-63].

3. DENDRIMERS

A covalently assembled molecule that forms a unique nanoparticle is called a dendrimer. Three unique architectural elements are present in dendrimers, specifically

- A core initiator.
- Internal layers (generations) that are profoundly connected to the internal core and made up of repeating units.
- The outermost interior generations are connected to the exterior (terminal functionality).

Dendrimers are artificial macromolecules at the nanoscale that have hyperbranched synthetic polymer systems and monodispersed topologies [64]. Because of their enhanced half-life, quick cellular entrance, high drug loading capacity, enhanced delivery efficiency, biocompatibility, targeting ability, stability, and decreased side effects, they are widely used as therapeutic carriers for neurological illnesses [65-66]. Dendrimers can be modified with linkages and conjugated with specific ligands to enhance targeted delivery to the CNS. A study using poly (amidoamine) dendrimers crosslinked with PEG hydrogel for the antidepressant, venlafaxine, showed sustained drug release and reduced toxicity due to the nanocarrier's swelling properties. The incorporation of PEG hydrogel improved the drug's sustained release profile and stability [67].

4. INSITU GEL:

In-situ gels are soft, stable, or solid-like materials consisting of a minimum of two components, one of which is a liquid. Once they arrive at a particular location, they gel because of coming into contact with bodily fluids or physicochemical changes such as pH, temperature, ionic concentration, UV light, or the presence of particular molecules or ions. In-situ gel drug delivery systems are mucoadhesive and involve gel formation at the site of action after formulation application. This process allows the drug to be delivered in a liquid or solution form, lengthening the time spent in the nasal cavity and decreasing the frequency of administration. It results in rapid absorption, onset of effect, reduced wastage of drugs, patient compliance, comfort, extended release of drugs, low dose, minimal drug accumulation, and increased bio-availability [68-69].

5. NANOSUSPENSION:

Polymeric nanosuspensions are NFs stabilized by lipid blends or nonionic surfactants. Among the benefits are enhanced drug loading, improved pharmacokinetics, ease of production, and the ability to modify the surface of polymeric nanosuspensions. For instance, modafinil (MDF) is an oral medication used to treat narcolepsy and attention deficit hyperactivity disorder (ADHD). The results showed that MDF functioned as an amorphous phase in the nanoparticle structure. Making NFs might be a practical strategy to enhance oral absorption [70].

6. MICELLE:

Micelles made of polymers that could act as nanoscale medication delivery systems. The self-assemblies of blocks of co-polymers are known as polymeric micelles. With promising drug and gene delivery nanocarriers, polymeric micelles have been created from biodegradable and biocompatible copolymer blocks for drug delivery. Core-shell structure is a characteristic of polymeric micelles [71-72]. The nasal absorption of peptides is enhanced by the combined micelles of fatty acids and bile salts [73].

7. NANOSTRUCTURED LIPID CARRIER:

High-pressure homogenization and the double emulsion approach (w/o/w) are commonly used to formulate NLCs [74]. To address the shortcomings of SLNs, a more recent generation of lipid-based NPs known as nanostructured lipid carriers (NLCs) was created. NLCs have a blend of liquid and solid lipids, which increases drug loading and inhibits burst release [75]. Higher encapsulation efficiency can be attained because hydrophobic molecules are more soluble in liquid lipid than solid lipid. NLC has certain drawbacks, such as comparatively inadequate ability to load drugs for hydrophilic medicines and reduced encapsulation efficiency for a mixture of two or more therapeutic agents [76-77].

8. SOLID LIPID NANOPARTICLES:

SLNs consist of a solid lipid matrix, surrounded by a surfactant layer, and contain lipophilic drugs. They are biocompatible, biodegradable, low toxicity, easy to produce, and have better control of drug release. However, SLNs have disadvantages like structural reorganization over time due to their single type of lipid, reducing the interior space for medicinal molecules and tightening the structure. To address this, NLCs have emerged, consisting of a solid lipid matrix and a liquid lipid. The addition of liquid lipids prevents crystallization and allows structural disorganization, creating larger spaces for drug molecules. Despite these advantages, because lipid nanoparticles can be passively diffused to the site of action, SLN is still an effective method [78-80].

9. POLYMERIC NANOPARTICLES:

Nanospheres and nanocapsules are two types of polymeric nanoparticles., depending on the preparation method and system characteristics. Nanocapsules have a reservoir system, containing the drug in a cavity surrounded by a single polymer membrane, while nanospheres are homogeneous matrix systems, uniformly dispersed or dissolved in the drug. Modulating the polymer allows for controlled drug release to reach desired therapeutic concentrations at the action site. These sub-micron particles contain active pharmaceutical substances, have high cell absorption potential, and can penetrate blood capillaries, improving bioavailability and drug accumulation [81]. Conjugating a ligand to the nanoparticles can change the antidepressant's specificity. They provide oral delivery, biodegradability, extended duration, sustained drug release, and excellent stability over time [82].

10. CARBON NANOTUBE:

One sheet of carbon atoms folded up into a cylindrical shape makes up a carbon nanotube. Because of their structural and chemical characteristics, CNTs make excellent drug delivery vehicles for the central nervous system [83]. The size, physical characteristics, and shape of the changed molecules are some of the factors that define the excellent biocompatibility and solubility of CNTs [84]. These factors impact the molecule's biocompatibility with the body, which in turn influences the therapeutic result. Because of their spherical shape, CNTs are able to entrap large amounts of drugs. Temperature affects the permeability of CNTs into brain cells; higher temperatures result in less permeability [85].

STRATEGIES TO ENHANCE DIRECT NOSE TO BRAIN DRUG DELIVERY:

One of the best ways to control the drug delivery characteristics of formulations is by surface engineering of the drug carrier, which involves interacting with a biological system through the surface coating. This tactic might determine the usefulness of this medication delivery method,

increasing its likelihood of success. The main research on surface modification of drug delivery/carrier systems to improve direct nose-to-brain medication delivery is highlighted in this section. The nasal cavity contains numerous obstacles that prevent different medications from being absorbed. Certain techniques have been effectively employed to enhance nasal medication absorption [86].

- **Structural modification:** Enhances drug structure without altering pharmacological activity.
- **Permeation enhancers:** Various categories like surfactants, fatty acids, phospholipids, cyclodextrins, bile salts, etc., are used to improve nasal absorption.
- **Particulate drug delivery:** Carriers like microspheres, liposomes, nanoparticles, and niosomes are used to prevent drug exposure to nasal environment and improve retention capacity.
- **Chemical penetration enhancers:** Solvents, Alkyl Methyl sulphoxides, Pyrrolidones, 1-Dodecyl azacycloheptan-2-one, and surfactants are widely used in nasal drug delivery.
- **Bio-adhesive polymer:** Increases drug retention time by creating an adhesive force between formulation and nasal mucosa.
- **Prodrug approach:** Inactive chemical moiety that becomes active at the target site to improve taste, odor, solubility, and stability.
- **Nasal enzyme inhibitors:** Minimize drug metabolism in nasal cavity by minimizing enzyme activity, including protease and peptidase.

ADVANTAGES AND DISADVANTAGES OF NOSE-TO-BRAIN DRUG DELIVERY USING NANOTECHNOLOGY

Table 1. :Advantages and Disadvantages of Nose-to-brain drug delivery [87-89]:

Advantages	Disadvantages
• Rapid drug absorption via highly vascularized mucosa.	• Limited delivery volume: 25-200 microliters.
• Large nasal surface area for dose absorption.	• Suitable for potent drugs: Limited volume.
• Noninvasive and easy administration.	• Low bioavailability: Low bioavailability.
• Good bioavailability of small drug molecules.	• Potential nasal irritation: Budesonide, Azelastine.
• Increased bioavailability of large drug molecules with absorption enhancers.	• Inability to deliver high molecular weight compounds: May decrease permeability.
• Alternative to parenteral route for proteins and peptides.	• Adverse effects: Pathological conditions can affect concentration.
• Convenient for long-term therapy.	• Limited understanding: Uncertainty in drug transport mechanisms.
• Reduces side effects due to low dose.	• Potential systemic toxicity: Unestablished due to absorption enhancers.
• Improves patient convenience and compliance.	• Reduced absorption surface area in compared to GIT.
• Self-administration possible.	• Potential mucosal toxicity: Enzymatic barrier to drug permeability.
• Direct transport into systemic circulation and CNS.	• Nasal congestion: Cold or allergic conditions can interfere.
•.Lower risk of overdose.	• Frequent use: May cause mucosal damage.
• No complex formulation requirements. • Doesn't require energy consumption	• Dosage loss: Possible due to improper administration technique.

CHALLENGES TO OVERCOME IN NANOPARTICLE-DERIVED TOXICITY TO NASAL MUCOSA:

Nanoparticle-derived harm to the nasal mucosa is a significant concern in drug-delivery systems. In order to reduce adverse effects and enhance safety, strategic methods are being employed. These include careful design and engineering of nanoparticle features, including size, surface qualities, and composition. Biocompatible materials and surface modifications are designed to minimize interactions that may cause inflammation or cellular stress [90]. Safety and biocompatibility are evaluated using in vitro investigations and animal models to understand cellular reactions, inflammatory responses, and potential effects on mucosal tissue integrity. This knowledge is used to make necessary modifications in nanoparticle design and composition to ensure safety while maintaining effectiveness [91]. A comprehensive approach includes careful preclinical evaluations, the addition of biodegradable components, and the tweaking of nanoparticle properties. This approach can help develop drug-delivery systems that target the brain through the nasal route while minimizing potential hazards to the delicate nasal mucosa [92].

CONCLUSIONS

Nanotechnology-based nose-to-brain drug delivery is a promising approach in psychiatric care, particularly for anxiety and depression. This method circumvents the blood-brain barrier, offering enhanced bioavailability, targeted drug delivery, reduced systemic side effects, and improved patient compliance. Various nanocarrier systems, including solid lipid nanoparticles, liposomes, polymeric nanoparticles, and dendrimers, have demonstrated remarkable potential in facilitating effective drug transport to the brain. However, challenges such as nanoparticle toxicity, mucosal irritation, and regulatory obstacles need to be overcome in order to guarantee clinical translation. Future research should focus on optimizing formulation stability, enhancing mucoadhesion, and conducting extensive in vivo and clinical studies. The integration of nanotechnology with nose-to-brain delivery holds immense promise for redefining psychiatric treatment and offering new hope to patients suffering from neuropsychiatric disorders. Various factors must be considered when developing nose-to-brain drug-delivery systems, including nasal architecture, mucociliary clearance, drug properties, formulation stability, and targeting efficiency. Alternative dosage forms, such as nanocarriers and nanogels, can be used for safer and more efficient nose-to-brain drug delivery. Targeting specificity and improving drug-delivery efficiency will revolutionize the future of neurological therapies. Recent studies have attempted to translate laboratory results into clinical applications, but little has been done in terms of optimizing and improving dosing efficiency. Limited volumes, differences in nasal anatomy, the need to create formulations and appropriate equipment, and overcoming nanoparticle-dependent toxicity to the brain tissue and nasal mucosa are some of the main obstacles.

REFERENCES

1. Collaborators GBDM. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*. (2022) 9(2):137-150.
2. Zhao YF, Verkhratsky A, Tang Y, Illes P. Astrocytes and major depression: the purinergic avenue. *Neuropharmacology*. (2022) 220:109252.

3. Gabriel FC, de Melo DO, Fráguas R, Leite-Santos NC, Mantovani da Silva RA, Ribeiro E. Pharmacological treatment of depression: a systematic review comparing clinical practice guideline recommendations. *PLoS ONE*. (2020) 15:e0231700.
4. Nemeroff CB. The state of our understanding of the pathophysiology and optimal treatment of depression: glass half full or half empty? *Am J Psychiatry*. (2020) 177:671-685.
5. Qian H, Shu C, Xiao L, Wang G. Histamine and histamine receptors: roles in major depressive disorder. *Front Psychiatry*. (2022) 13:825591.
6. Jiang Y, Zou D, Li Y, Gu S, Dong J, Ma X, Xu S, Wang F, Huang JH. Monoamine neurotransmitters control basic emotions and affect major depressive disorders. *Pharmaceuticals*. (2022) 15:1203.
7. Lenox RH, Frazer A. Mechanism of action of antidepressants and mood stabilizers. In: *Neuropsychopharmacology: The Fifth Generation of Progress*. American College of Neuropsychopharmacology: Phoenix, AZ, USA; (2002) pp. 1139-1163. ISBN 9780781728379.
8. Kircanski K, Joormann J, Gotlib IH. Cognitive aspects of depression. *Wiley Interdiscip Rev Cogn Sci*. (2012) 3:301-313.
9. Wiedmann TS. Pharmaceutical Inhalation Aerosol Technology, A.J. Hickey (Ed.). Marcel Dekker, New York (2004), 603 pp. *Journal of Controlled Release*. (2005) 105:177-178.
10. Sharma PK, Chaudhari P, Kolsure P, Ajab A, Varia N. Recent trends in nasal drug delivery system - An overview. *ARPB*. (2006) 5:4.
11. Ramadan HH, Sanclement JA, Thomas JG. Chronic rhinosinusitis and biofilms. *Otolaryngol Head Neck Surg*. (2005) 132:414-417.
12. Mahita B, Vinod K. A clinicopathological study of allergic rhinitis. *Asian J Pharm Clin Res*. (2017) 10:186-191.
13. Alexander A, Agrawal M, Uddin A, Siddique S, Shehata AM, Shaker MA, Ata Ur Rahman S, Abdul MIM, Shaker MA. Recent expansions of novel strategies towards the drug targeting into the brain. *Int J Nanomed*. (2019) 14:5895–5909.
14. Engelhardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: Function and dysfunction. *Semin Immunopathol*. (2009) 31:497–511.
15. Koutsari C, Dilworth TJ, Holt J, Elshaboury R, Rotschafer JC. Central Nervous System Infections. In: *Pharmacotherapy: A Pathophysiologic Approach, 11e*. DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, Eds.; McGraw-Hill Education: New York, NY, USA, 2020.
16. Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, Ajazuddin, Ravichandiran V, Murty US, Alexander A. Recent strategies and advances in the fabrication of nano lipid carriers and their application towards brain targeting. *J Control Release*. (2020) 321:372–415.
17. Béduneau A, Saulnier P, Benoit JP. Active targeting of brain tumors using nanocarriers. *Biomaterials*. (2007) 28:4947–4967.
18. Goldmann E. Vitalfärbung am Zentralnervensystem: Beitrag zur Physiopathologie des Plexus chorioideus und der Hirnhaute, 1913.
19. Costa CP, Moreira JN, Sousa Lobo JM, Silva AC. Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: a current overview of in vivo studies. *Acta Pharm Sin B*. (2021) 11:925–940.
20. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic

challenges during drug development. *Drug Deliv Transl Res*. (2021).
21. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Curr Drug Deliv*. (2012) 9:566–582.
22. Dahl R, Mygind N. Anatomy, physiology and function of the nasal cavities in health and disease. *Adv Drug Deliv Rev*. (1998) 29:3–12.
23. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. *Int J Pharm*. (2009) 379(1):146-157.
24. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: An anatomic, physiologic, and delivery technology overview. *Ther Deliv*. (2014) 5:709–733.
25. Khunt D, Misra M. Chapter 1—An overview of anatomical and physiological aspects of the nose and the brain. In: Pardeshi CV, Souto EB, editors. *Direct Nose-to-Brain Drug Delivery*. Academic Press; Cambridge, MA, USA: 2021. pp. 3–14.
26. Yadav HKS, Lim-Dy A, Pathak YV. An overview of the anatomy and physiology of nasal passage from drug delivery point of view. In: Pathak YV, Yadav HKS, editors. *Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions*. Springer International Publishing; Cham, Switzerland: 2023. pp. 1–13.
27. Maigler F, Ladel S, Flamm J, Gänger S, Kurpiers B, Kiderlen S, et al. Selective CNS targeting and distribution with a refined region-specific intranasal delivery technique via the olfactory mucosa. *Pharmaceutics*. (2021) 13(11):1904.
28. Harkema JR, Carey SA, Wagner JG. The nose revisited: A brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. *Toxicol Pathol*. (2006) 34(3):252–269.
29. Feng Y, He H, Li F, Lu Y, Qi J, Wu W. An update on the role of nanovehicles in nose-to-brain drug delivery. *Drug Discov Today*. (2018) 23(5):1079–1088.
30. Field PM, Li Y, Raisman G. Ensheathment of the olfactory nerves in the adult rat. *J Neurocytol*. (2003) 32(3):317–324.
31. Banks WA, During MJ, Niehoff ML. Brain uptake of the glucagon-like peptide-1 antagonist exendin(9-39) after intranasal administration. *J Pharmacol Exp Ther*. (2004) 309:469-475.
32. Pardeshi CV, Belgamwar VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: An excellent platform for brain targeting. *Expert Opin Drug Deliv*. (2013) 10:957-972.
33. Terrier LM, Hadjikhani N, Destrieux C. The trigeminal pathways. *J Neurology*. (2022) 269(7):3443–3460.
34. Schaefer ML, Bottger B, Silver WL, Finger TE. Trigeminal collaterals in the nasal epithelium and olfactory bulb: A potential route for direct modulation of olfactory information by trigeminal stimuli. *J Comp Neurology*. (2002) 444(3):221–226.
35. Tucker D. Nonolfactory responses from the nasal cavity: Jacobson's organ and the trigeminal system. In: Beidler LM, editor. *Olfaction*. Handbook of Sensory Physiology, vol 4 / 1. Springer, Berlin, Heidelberg; 1971.
36. Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanism and experimental considerations. *J Pharm Sci*. (2010) 99(4):1654-1673.
37. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience*. (2004) 127(2):481-496.

38. Pardridge WM. Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab*. (2012) 32(11):1959-1972.
39. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier by nanoparticles. *J Control Release*. (2012) 161(2):264-273.
40. Zhang Y-B, Xu D, Bai L, Zhou Y-M, Zhang H, Cui Y-L. A review of non-invasive drug delivery through respiratory routes. *Pharmaceutics*. (2022) 14:1974.
41. Rehman S, Nabi B, Pottoo FH, Baboota S, Ali J. Lipid nanoformulations in the treatment of neuropsychiatric diseases: an approach to overcome the blood-brain barrier. *Curr Drug Metab*. (2020) 21:674–684.
42. Jacob S, Nair AB, Shah J, Gupta S, Boddu SHS, Sreeharsha N, Joseph A, Shinu P, Morsy MA. Lipid nanoparticles as a promising drug delivery carrier for topical ocular therapy—An overview on recent advances. *Pharmaceutics*. (2022) 14:533.
43. Tzeyung AS, Md S, Bhattamisra SK, Madheswaran T, Alhakamy NA, Aldawsari HM, Radhakrishnan AK. Fabrication, optimization, and evaluation of rotigotine-loaded chitosan nanoparticles for nose-to-brain delivery. *Pharmaceutics*. (2019) 11:26.
44. Khatri DK, Preeti K, Tonape S, Bhattacharjee S, Patel M, Shah S, Singh PK, Srivastava S, Gugulothu D, Vora L, et al. Nanotechnological advances for nose to brain delivery of therapeutics to improve Parkinson therapy. *Curr Neuropharmacol*. (2023) 21:493–516.
45. Gómez-Hens A, Fernández-Romero JM. Analytical methods for the control of liposomal delivery systems. *Trends Anal Chem*. (2006) 25:167–178.
46. Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid nanoparticles from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano*. (2021) 15:16982–17015.
47. Dow S. Liposome-nucleic acid immunotherapeutics. *Expert Opin Drug Deliv*. (2008) 5:11–24.
48. Garbuzenko OB, Mainelis G, Taratula O, Minko T. Inhalation treatment of lung cancer: The influence of composition, size and shape of nanocarriers on their lung accumulation and retention. *Cancer Biol Med*. (2014) 11:44–55.
49. Shah V, Taratula O, Garbuzenko OB, Patil ML, Savla R, Zhang M, Minko T. Genotoxicity of different nanocarriers: Possible modifications for the delivery of nucleic acids. *Curr Drug Discov Technol*. (2013) 10:8–15.
50. Sanchez-Purra M, Ramos V, Petrenko VA, Torchilin VP, Borros S. Double-targeted polymersomes and liposomes for multiple barrier crossing. *Int J Pharm*. (2016) 511:946–956.
51. Dhaliwal HK, Fan Y, Kim J, Amiji MM. Intranasal delivery and transfection of mRNA therapeutics in the brain using cationic liposomes. *Mol Pharm*. (2020) 17:1996–2005.
52. Al Asmari AK, Ullah Z, Tariq M, Fatani A. Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. *Drug Des Devel Ther*. (2016) 10:205–215.
53. Mutlu NB, De˘gim Z, Yilmaz S, E¸ssiz D, Nacar A. New perspective for the treatment of Alzheimer's disease: Liposomal rivastigmine formulations. *Drug Dev Ind Pharm*. (2011) 37:775–789.
54. Hoekman JD, Srivastava P, Ho RJ. Aerosol-stable peptide-coated liposome nanoparticles: A proof-of-concept study with opioid fentanyl in enhancing analgesic effects and reducing

plasma drug exposure. *J Pharm Sci*. (2014) 103:2231–2239.
55. Migliore MM, Vyas TK, Campbell RB, Amiji MM, Waszczak BL. Brain delivery of proteins by the intranasal route of administration: A comparison of cationic liposomes versus aqueous solution formulations. *J Pharm Sci*. (2010) 99:1745–1761.
56. Zheng X, Shao X, Zhang C, Tan Y, Liu Q, Wan X, Zhang Q, Xu S, Jiang X. Intranasal H102 peptide-loaded liposomes for brain delivery to treat Alzheimer's disease. *Pharm Res*. (2015) 32:3837–3849.
57. Pashirova TN, Zueva IV, Petrov KA, Lukashenko SS, Nizameev IR, Kulik NV, Voloshina AD, Almasy L, Kadirov MK, Masson P, et al. Mixed cationic liposomes for brain delivery of drugs by the intranasal route: The acetylcholinesterase reactivator 2-PAM as encapsulated drug model. *Colloids Surf B Biointerfaces*. (2018) 171:358–367.
58. Bhosale RR, Osmani RA, Ghodake PP, Shaikh SM, Chavan SR. Nanoemulsion: A review on novel profusion in advanced drug delivery. *Indian J Pharm Biol Res*. (2014) 2(1):122–127.
59. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: An advanced mode of drug delivery system. *3 Biotech*. (2015) 3(5):123–127.
60. Patel ZS, Shah R, Shah DN. Nanoemulsion: An innovative approach for topical delivery. *Pharma Sci Monitor*. (2016) 7(2):21–36.
61. Lombardo R, Musumeci T, Carbone C, Pignatello R. Nanotechnologies for intranasal drug delivery: An update of literature. *Pharm Dev Technol*. (2021) 26:824–845.
62. Xu J, Tao J, Wang J. Design and application in delivery system of intranasal antidepressants. *Front Bioeng Biotechnol*. (2020) 8:626882.
63. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK. Nanoemulsion: Concepts, development and applications in drug delivery. *J Control Release*. (2017) 252:28–49.
64. Sherje AP, Jadhav M, Dravyakar BR, Kadam D. Dendrimers: A versatile nanocarrier for drug delivery and targeting. *Int J Pharm*. (2018) 548:707–720.
65. Parajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC. Potential application of dendrimers in drug delivery: A concise review and update. *J Drug Deliv Ther*. (2016) 6:71–85.
66. Xu L, Zhang H, Wu Y. Dendrimer advances for the central nervous system delivery of therapeutics. *ACS Chem Neurosci*. (2013) 5:2–13.
67. Florendo M, Figacz A, Srinageshwar B, Sharma A, Swanson D, Dunbar GL, Rossignol J. Use of polyamidoamine dendrimers in brain diseases. *Molecules*. (2018) 23:2238.
68. Sarada K, Firoz S, Padmini K. In-situ gelling system: A review. *Int J Curr Pharma Rev Res*. (2014) 15(4):76–90.
69. Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. *J Controlled Release*. (2002) 80(1-3):9–28.
70. Adibkia K, Selselehjonban S, Emami S, Osouli-Bostanabad K, Barzegar-Jalali M. Electrosprayed polymeric nanobeads and nanofibers of modafinil: preparation, characterization, and drug release studies. *Bioimpacts*. (2019) 9:179–88.
71. Kwon GS, Okano T. Polymeric micelles as new drug carriers. *Adv Drug Deliv Rev*. (1996) 21:107-116.
72. Nishiyama N, Kataoka K. Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug

and gene delivery. *Pharmacol Ther*. (2006) 112:630-648.

73. Tengamnuay P, Mitra AK. Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength, adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2] kyotorphin. *Pharm Res*. (1990) 7(2):127-133.
74. Martins S, Sarmento B, Ferreira DC, Souto EB. Lipid-based colloidal carriers for peptide and protein delivery–liposomes versus lipid nanoparticles. *Int J Nanomedicine*. (2007) 2:595–607.
75. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. *Indian J Pharm Sci*. (2009) 71:349–358.
76. Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, Ajazuddin, Ravichandiran V, Murty US, Alexander A. Recent strategies and advances in the fabrication of nano lipid carriers and their application towards brain targeting. *J Control Release*. (2020) 321:372–415.
77. Tapeinos C, Battaglini M, Ciofani G. Advances in the design of solid lipid nanoparticles and nanostructured lipid carriers for targeting brain diseases. *J Control Release*. (2017) 264:306–332.
78. Teixeira MI, Lopes CM, Amaral MH, Costa PC. Surface-modified lipid nanocarriers for crossing the blood-brain barrier (BBB): A current overview of active targeting in brain diseases. *Colloids Surf B Biointerfaces*. (2023) 221:112999.
79. Lombardo R, Musumeci T, Carbone C, Pignatello R. Nanotechnologies for intranasal drug delivery: An update of literature. *Pharm Dev Technol*. (2021) 26:824–845.
80. Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid nanoparticles from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano*. (2021) 15:16982–17015.
81. Kulthe SS, Choudhari YM, Inamdar NN, Mourya V. Polymeric micelles: Authoritative aspects for drug delivery. *Des. Monomers Polym.* (2012) 15:465–521.
82. Neha B, Ganesh B, Preeti K, Guru S. Drug delivery to the brain using polymeric nanoparticles: A review. *Int. J. Pharm. Life Sci.* (2013) 2:107–121.
83. Medyantseva, E.P.; Brusnitsyn, D.V.; Varlamova, R.M.; Maksimov, A.A.; Konovalova, O.A.; Budnikov, H.C. Surface modification of electrodes by carbon nanotubes and gold and silver nanoparticles in monoaminoxidase biosensors for the determination of some antidepressants. *J. Anal. Chem.* 2017, 72, 362–370.
84. Soni, S.; Ruhela, R.K.; Medhi, B. Nanomedicine in Central Nervous System (CNS) disorders: A present and future prospective. *Adv. Pharm. Bull.* 2016, 6, 319–335.
85. Saeedi, M.; Eslamifar, M.; Khezri, K.; Dizaj, S.M. Applications of nanotechnology in drug delivery to the central nervous system. *Biomed. Pharmacother.* 2019, 111, 666–675.
86. Ibrahim, A.; Alsarra, A.Y.; Hamed, F.; Fars, K.A.; Maghraby, E.G. Vesicular systems for intranasal drug delivery. In *Drug Delivery to the Central Nervous System*, K.K. Jain (Ed.), *Neuromethods* 45.
87. Singhkumar, A. Nasal cavity: A promising transmucosal platform for drug delivery and research approach from nasal to brain targeting. *Journal of Drug Delivery and Therapeutics* 2012, 2(3), 22-33.
88. Chhajed, S.; Sangle, S.; Barhate, S. Advantagious Nasal Drug Delivery System: A Review. *International Journal of Pharmaceutical Science and Research* 2011, 2(6), 1322-1336.

89. Zaheer, A.; Sachin, S.; Swamy. Mucoadhesive Polymers: Drug Carriers for Improved Nasal Drug Delivery. *Indian Journal of Novel Drug Delivery* 2012, 4(1), 2-16.
90. Kumar, A.; Pandey, A.N.; Jain, S.K. Nasal-nanotechnology: Revolution for efficient therapeutics delivery. *Drug Deliv.* 2016, 23, 681–693.
91. Barua, S.; Mitragotri, S. Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects. *Nano Today* 2014, 9, 223–243.

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