

A Comprehensive Review on Intranasal Nanomedicine for CNS Disorders

Lalit Kumar¹, Ms. Ravina Naik²

¹Student, Abhilashi College of Pharmacy, Nerchowk, Mandi 175008 (H.P)

²Assistant Professor, Abhilashi College of Pharmacy, Nerchowk, Mandi 175008 (H.P)

Corresponding Author: Lalit Kumar

Date of Submission: 05-03-2026

Date of Acceptance: 15-03-2026

ABSTRACT

Addressing the primary restriction imposed by the blood–brain barrier, intranasal nanomedicine has become a viable method for the targeted delivery of therapeutics to the central nervous system (CNS). Recent developments in nose-to-brain delivery systems enabled by nanotechnology are highlighted in this review, along with their possible uses in neurological and psychiatric conditions. The nasal route reduces systemic exposure while facilitating direct drug delivery to the brain by offering a non-invasive pathway through the olfactory and trigeminal nerves. Numerous nanocarriers have been shown to improve drug stability, controlled release, and brain bioavailability. These include polymeric nanoparticles, lipid-based systems, dendrimers, nanoemulsions, and nanogels. By overcoming mucociliary clearance and enzymatic degradation, formulation techniques like mucoadhesive polymers, permeation enhancers, enzyme inhibitors, and stimuli-responsive gels further maximize therapeutic efficacy. Preclinical results point to great promise for treating conditions like depression, glioblastoma, epilepsy, Parkinson's disease, and Alzheimer's disease. Clinical translation is still hampered by issues with long-term safety, nasal absorption variability, and large-scale manufacturing, despite encouraging advancements. The successful use of intranasal nanomedicine for CNS therapies may be accelerated by future advancements centered on personalized medicine, sophisticated formulation design, and regulatory standardization. All things considered, this developing field offers a revolutionary strategy for enhancing neurotherapeutic accuracy and efficacy.

Key Words: Intranasal Drug Delivery, Nanomedicine, CNS Disorders, Nanocarriers, BBB

I. INTRODUCTION:

Currently, a wide range of brain disorders is categorized as deficits within both the neurological and psychiatric domains, resulting in

both short-term and long-term disabilities [1]. These deficits arise from either inherent brain dysfunction or the interaction of environmental factors with the brain [2]. CNS disorders are types of neurological problems that affect how the brain or spinal cord works or looks. CNS diseases include Alzheimer's disease, Parkinson's disease, dementia, epilepsy, stroke, multiple sclerosis, encephalopathy, and other cerebrovascular diseases [3]. Even though a lot of research has been done on how diseases start and how to treat them, there are still not many new drugs approved for disorders affecting the central nervous system compared to other types of diseases. Recently, the US FDA fast-tracked the approval of aducanumab-avwa (Aduhelm™, made by Biogen Inc. in Massachusetts, USA), which is the first and only treatment available for Alzheimer's disease. However, it is still pending approval until confirmatory trials are completed [4]. Over one-third of the global population experiences a condition that affects the functioning of the nervous system, resulting in a total health loss of 443 million disability-adjusted life-years (DALYs) in 2021 [5]. More than half of patients with substance use disorder (SUD) have concurrent psychiatric comorbidity, such as mood disorders, anxiety disorders, personality disorders, and substance-induced psychosis, according to a number of clinical and epidemiological studies. This comorbidity has been repeatedly linked to worse clinical outcomes, more severe symptoms, a lower quality of life, more medical complications, and restricted access to treatment services. Additionally, the presence of psychiatric disorders increases the risk of clinical complications and impedes treatment program compliance and effectiveness in patients with SUD and significant medical comorbidity, such as HIV infection or hepatitis B and C. This highlights the need for comprehensive approaches that concurrently address addictive, psychiatric, and medical aspects [6,7]. Over the years, these tiny drug delivery

systems have gone from basic lipid-based capsules to advanced, multi-functional nanocarriers that have special features allowing them to deliver drugs to specific places in the body, release them at the right time, and help make various drugs, such as nucleic acids and proteins, more effective [8,9]. Among these, liposomes, which are water-filled spaces enclosed by a layer of fat, are an important type of structure. clinically successful drug delivery vehicles. Today, 15 different liposomal drug forms have been approved by the Food and Drug Administration, are sold on the market, and are being used in medical treatments [10]. Lipid-based nanocarriers are considered highly effective for gene delivery because they can efficiently package, safeguard, and transport nucleic acids. Advances, including the addition of targeting ligands, materials that react to specific stimuli, and changes to the surface, have enabled these lipid nanocarriers to engage with biological systems more accurately [11,12]. The main objectives of specialized drug delivery system are to prolong drug presence, confine it to a specific area, direct it towards diseased tissue, and interact with that tissue, all while ensuring patient safety [13]. The primary obstacle driving advancements in brain drug delivery technology is the existence of the blood-brain barrier (BBB), which significantly restricts the creation of novel brain medications. This barrier prevents over 98% of small molecule drugs from entering the brain, as demonstrated by the limited uptake of histamine, a small molecule drug weighing only 111 Daltons, in the mouse brain [14]. Variations in individual drug responses and BBB permeability highlight the necessity for personalized drug delivery methods. To enhance treatment effectiveness and safety, it is crucial to include patient-specific information, such as genetic markers and imaging findings, in the development of drug delivery systems. This tailored medicine strategy has the capability to transform CNS drug treatment [15]. The problem of tissue penetration from the site of entrance into the brain to target cells or areas of interest inside the brain persists even if therapies are able to cross the blood-CSF barrier or the BBB, or if they are given locally to get around these barriers. Penetration inside the brain parenchyma is a frequently disregarded yet significant barrier to medication delivery into the central nervous system (CNS), given the focus of the neurotherapeutic field on bypassing the BBB [16]. The olfactory and trigeminal nerves are the main sources of intranasal drug delivery, which uses both intracellular and extracellular transport channels to provide direct

access to the central nervous system [17]. Drugs provided by the trigeminal nerve go to the brainstem through the anterior lacerated foramen, whereas drugs administered via the olfactory pathway travel through the cribriform plate to reach the olfactory bulb and other brain areas [18]. PNPs, SLNS, liposomes, and micelles were employed as nanocarriers in the medical profession over the first several decades. However, more recent and sophisticated nano-systems, such as dendrimers, nanoemulsions, nano gels, and nanosuspensions, are currently the focus of this nanotechnology approach [19]. Biofunctionalized carbon nanotubes (CNTs) have recently emerged as a viable tool because of their mechanical, structural, and surface chemical variety as well as their capacity to penetrate cells [20]. Thus, intranasal nanomedicine has drawn a lot of attention as a cutting-edge technique to improve brain targeting and get beyond the obstacles preventing CNS treatment. In addition to discussing potential future paths for their therapeutic application in CNS illnesses, this study provides an overview of recent developments in nano-based intranasal delivery systems.

Anatomy & Physiology of Nasal Cavity

A ground-breaking idea in pharmaceutical research, the nose-to-brain medicine delivery system provides a novel means of delivering medicinal chemicals straight from the nasal cavity to the brain [21]. The external nose and the nasal cavity, which are both essential for respiratory function, make up the intricate system known as the nasal architecture. The visible aperture for inhaling air is the external nose, which is made of bone and cartilage. It becomes the main route for respiratory function after it enters the nasal cavity, which is divided by the nasal septum [22,23,24]. The brain "meets the outside world" exclusively in the nose. Nerve filaments, or axons, of the 12th cranial nerve (the olfactory nerve) extend directly from the olfactory bulb in the limbic region of the brain to the upper posterior segments of the nose, penetrate the mucosal lining and allow direct contact with the environment without a peripheral sensory receptor relay. There are millions of these neurons that function as chemical sensors, pick up food odors, and influence social behaviors. These peculiar neurons were once thought to be the sole type of neurons that could regenerate. Additionally, this special and significant anatomical configuration provides a possible pathway for direct drug delivery into the central nervous system [18,25,26]. The external nose and the nasal cavity, which are both essential for respiratory function,

make up the intricate system known as the nasal architecture. The visible aperture for inhaling air is the external nose, which is made of bone and cartilage. It becomes the main route for respiratory

function after it enters the nasal cavity, which is divided by the nasal septum [22,23,24].

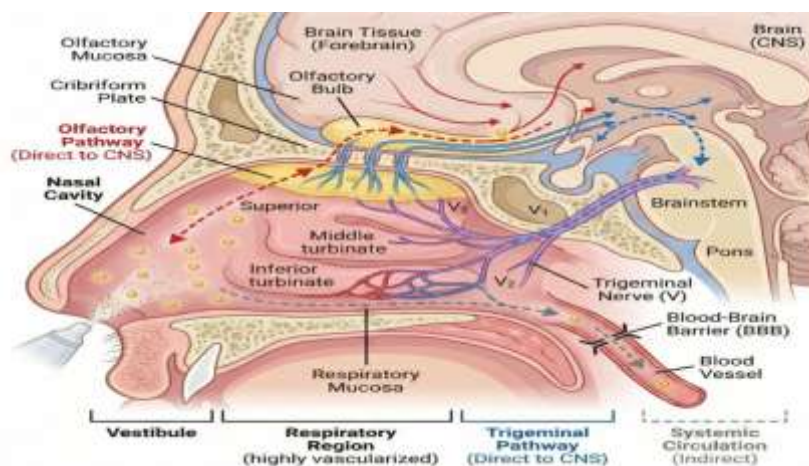


Figure 1 : Anatomical pathways for intranasal nanomedicine delivery to the CNS

Barriers to intranasal CNS Delivery

1. Blood–Brain Barrier (BBB) as a Major Limitation

The development of effective therapies for central nervous system (CNS) disorders remains challenging due to the blood–brain barrier (BBB), which restricts the entry of many therapeutic agents into the brain [27]. This limitation has increased interest in intranasal (IN) drug delivery as a non-invasive approach that may enable direct nose-to-brain transport and reduce reliance on systemic BBB penetration [27,28].

2. Drug-Related Barriers: Molecular Weight and Physicochemical Properties

Drug absorption across the nasal mucosa is strongly dependent on molecular size and physicochemical characteristics. Small lipophilic drugs (MW < 1 kDa) are generally absorbed more efficiently, whereas large hydrophilic molecules (MW > 1 kDa), including peptides and proteins, show low permeability across the nasal epithelium [29,30]. IN bioavailability is inversely related to molecular weight and also depends on the dominant absorption mechanism [33].

3. Biochemical Barriers: Nasal Metabolism and Enzymatic Degradation

Intranasally administered drugs may undergo enzymatic degradation and metabolism within the nasal mucosa, thereby decreasing the

fraction of intact drug available for absorption. This is particularly relevant for biologics and labile compounds, which are more prone to enzymatic breakdown and reduced stability in the nasal environment [29,32].

4. Clearance Barriers: Mucociliary Clearance and Short Residence Time

Mucociliary clearance is one of the most important physiological barriers limiting IN drug delivery. It rapidly removes administered formulations from the nasal cavity, leading to short residence time and insufficient contact with the absorptive epithelium [31,32]. This results in reduced absorption and variable therapeutic outcomes.

5. Anatomical and Physiological Barriers Affecting Nose-to-Brain Transport

Several nasal anatomical and physiological factors restrict efficient deposition and transport of drugs to the CNS. These include the nasal vestibule and nasal valve, limited access to the olfactory region, and epithelial tight junctions that restrict paracellular passage [32]. In addition, efflux transporters may reduce drug uptake by actively transporting compounds back into the nasal lumen, contributing to low and variable delivery efficiency across individuals [34]. Overall variability in deposition and uptake

remains a challenge in translational application [28,34].

Evidence and Mechanisms Supporting Nose-to-Brain Transport

Despite these limitations, evidence suggests that certain drugs can be transported

directly from the nasal cavity to the cerebrospinal fluid (CSF), supporting the feasibility of the nose-to-brain route and encouraging the development of optimized intranasal delivery systems for CNS targeting [35].



Figure 2 : Evidence and mechanisms supporting Nose-to-Brain Transport

Rationale of Nanomedicine for Intranasal CNS Targeting

Neurodegenerative and neurodevelopmental disorders affect a substantial global population and remain difficult to treat due to restricted drug transport across the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier. Intranasal delivery has emerged as a promising strategy to enhance CNS targeting by enabling nose-to-brain transport and improving brain exposure. In this context, nano-based systems—particularly polymeric nanoparticles—have attracted increasing attention due to their ability to improve drug bioavailability in the brain and their flexibility in formulation design [36]. Because nanomedicines have a promising function in CNS drug delivery, these days, imaging agents and therapies for CNS illnesses heavily rely on them. It has been demonstrated that nanomedicines may actively and successfully infiltrate the damaged brain tissues and breach the blood–brain barrier. Moreover, enhanced strength, stability, surface area, and sensitivity are linked to nanomedicines [37,38]. Plasticity and changing surface properties, flexibility, and controlled release of the active therapeutic substance are all hallmarks of nano-preparations. Active drugs designed especially for the central nervous system (CNS) are delivered to the brain using nanotherapeutics [39]. Because of its increased bioavailability in the brain, intranasal (IN) medication delivery has shown itself to be a major advantage over other drug administration methods. IN drug administration has solved this issue since the BBB keeps different drugs from getting to the

brain. By blocking the majority of external chemicals, including lipids, peptides, and essential nutrients, from entering the brain, the blood–brain barrier (BBB) preserves the balance of the brain. As a result, almost all medicines and chemicals have difficulties accessing the brain [40].

Types of Nanocarriers Used in Intranasal Delivery Polymeric nanoparticles

The size range of polymeric nanoparticles is 1–999 nm. Polymeric NPs are made from synthetic polymers or copolymers of poly (D, L-lactic acid) (PLA), poly(ϵ -caprolactone) (PCL), PLGA, or natural polymers such chitosan and maltodextrins. Using techniques like solvent evaporation, nanoprecipitation, super critical fluid technology, and hot or cold homogenization, two or more chains of block copolymers with different hydrophobicity self-assemble to form them [41,42]. Bulk matrix breakdown is how drugs are released; however, the pace of polymer degradation may be influenced by a variety of environmental conditions, including pH and the physicochemical properties of NPs. As a result, the release pattern might vary but usually has a biphasic profile [43].

Lipid based nanocarriers

Liposomes: Liposomes are nanometric vesicles made of lipids [44]. Liposomes and the cell membrane fuse to deliver the medication within the cell. While the lipid bilayer can regulate and manage the drug's release and absorption to accomplish the effect of prolonged release, encasing the medication in liposomes can lessen the direct contact between the drug and nasal

mucosa. They have a variety of applications and may encapsulate both hydrophilic and lipophilic compounds. Numerous pre-clinical investigations have demonstrated that nasally administered liposomal formulations can improve medication usage and reduce systemic adverse effects by increasing the effectiveness of drug transport into the brain [31,45,46].

Nanoemulsions : Nanoemulsions (NEs) are nano-scale colloidal systems that typically have particle sizes between 20 and 200 nm and consist of an oil phase, an aqueous phase, and a surfactant. Water-in-oil, oil-in-water, and bicontinuous nanoemulsions are the three different kinds of nanoemulsions. Take use of their exceptional capacity to boost drug solubility, offer a sizable surface area for drug absorption, and make preparation simple [47]. NEs have drawn a lot of interest. Excipients in NEs can help them pass past the nasal epithelium and reach the brain, according to earlier research. For instance, chitosan can increase the amount of time that NEs stay in the nasal cavity and facilitate the transfer of medications from the nose to the brain [48].

Nanostructured lipid carriers : Lipid nanoparticles known as nanostructured lipid carriers (NLCs) have been created recently to address the shortcomings of SLNs [47]. It is made up of both liquid and solid lipids [49]. Physiological lipids such mono-, di-, and triglycerides, fatty acids, and waxes are used to make NLCs less toxic and more stable [50].

Dendrimers

Dendrimers, which are nanosized macromolecules with a hyperbranched globular shape, are frequently employed in drug delivery. Dendrimers feature distinct chemical structures and monodispersity when compared to conventional polymer nanovehicles. Furthermore, dendrimers' unique structure gives them the ability to load medicinal medicines via electrostatic adsorption or covalent conjugation [51]. Dendrimers resemble a multitude of biological entities in size. For instance, generation 5 (G5) polyamidoamine (PAMAM) dendrimers have nearly the same size and shape as hemoglobin (5.5 nm in diameter) [52]. Given that most dendrimers are uniformly modest in size and that smaller nanoparticles pass through the BBB more quickly than larger ones [53,54]. It has been demonstrated that brain uptake, diffusion, and specific cellular uptake of dendrimers are determined by both dendrimer physicochemical features and disease pathophysiology. According to reports, in an ischemic stroke scenario, PAMAM

smaller than 11 nm is unnecessary for crossing the compromised BBB [55]. Drugs loaded into dendrimers would have significant impacts once they reach the site of illness or even certain cells that cause neuroinflammation, such as astrocytes and microglia. To treat cerebral palsy, for example, scientists created a dendrimer-N-acetyl-L-cysteine nanoconjugate (D-NAC) [56].

Hydrogels & Nanogels

Hydrogel compositions with sufficient rheological qualities are challenging to give with a typical nasal spray device, however this can be addressed utilizing in situ gelation [57]. The nasal delivery of medications has made extensive use of in situ gelling hydrogels. These formulas are given as a solution. Once in the nasal mucosa, a trigger like pH or temperature causes the polymer's structure to change, forming a hydrogel. When mucoadhesive agents like chitosan and hydroxypropyl methylcellulose are combined with stimulus-sensitive polymers like poloxamers and poly (N- isopropyl acrylamide), the formulation's electrostatic attraction to the nasal cavity's mucus is enhanced [57,58]. Nanogels have been created for the intranasal delivery of medications to treat lifestyle illnesses, as carriers for vaccines, and to treat brain disorders including migraines, depression, and Alzheimer's disease, among others. Both hydrophilic and hydrophobic medications may be administered via nanogels, and because they can cross the blood-brain barrier when administered intranasally, they can be utilized to treat brain disorders. When compared to the administration of free drug, the use of nanogels for drug delivery has been shown to be more successful because to factors including less drug toxicity, increased drug cellular absorption, high drug loading, and controlled release of the loaded drug at the intended spot [59,60,61,62,63].

Formulation strategies for intranasal nanomedicine Mucoadhesive strategies

A crucial physiological process that severely hampers nose-to-brain transfer is the clearance of the mucociliary system. Therefore, NP-based formulations able to interact with mucin and lengthen their staying duration in the smell area have been explored for ages [64]. In this context, chitosan NP or polymer NP encapsulated with this polymer has become a staple in between the nose and the brain delivery [65]. Because of its abundance of blood arteries and microvilli, the nasal mucosa greatly increases the surface area available for drug absorption and offers an

effective route for medications to reach the circulation [66,67,68]. Additionally, the olfactory epithelium, linked to several brain areas through the olfactory and trigeminal nerves, acts as an essential pathway for delivering drugs to the brain. This link not only facilitates focused delivery to particular areas of the brain but also permits accurate treatment of different neurological disorders [69,70,71]. Chitosan, a product of chitin deacetylation, serves as a cornerstone material in the development of modern biomedical delivery vehicles [72]. Chitosan-based nanoparticles exhibit strong mucoadhesive characteristics owing to their cationic surface charge and enable prolonged, sustained release of the incorporated drug [73,74]. It has been discovered that chitosan is biocompatible because human enzymes, such as lysozyme, can break it down [75]. Its hydroxyl and amino groups also facilitate chemical modification. By altering the DDA and molecular weight of chitosan, it is possible to vary the electrostatic contact between chitosan and mucosal membranes [76].

Permeation Enhancers

Drugs with high molecular weights have been studied for improved absorption using permeation enhancers. Increased membrane fluidity and tight junction permeability, the creation of hydrophilic pores, and a decrease in viscosity and enzymatic activity are some of the suggested processes [30]. Insulin transport into the rat brain was improved by the cell-penetrating peptide penetratin [77]. Cyclodextrins, surfactants, saponins, fusidic acids, phospholipids, bile salts, laurth-9-sulfate, and fatty acids are examples of frequently used permeation enhancers [78]. Furthermore, aside from increasing adherence and extending staying duration in the nasal mucosa, mucoadhesive compounds like chitosan have been demonstrated to improve penetration by opening tight junctions. To increase the absorption of medications with high molecular weight, permeation enhancers have been investigated. Increased membrane fluidity and tight junction permeability, hydrophilic pore formation, and decreased viscosity and enzyme function are some of the suggested explanations [30]. Permeation enhancers can, in general, stop inadequate nasal absorption of proteins, peptides, and other macromolecules; however, their advantages must be carefully balanced to preserve patient safety and tolerability, particularly over an extended period of time.

Enzyme inhibitors for peptide/protein drugs

For nasal medication administration, enzymatic degradation is still another important constraint, especially for proteins and peptides. Reduced bioavailability of these compounds is a major effect of this frequently disregarded issue. Enzymes such as exopeptidases, which include mono- and diaminopeptidases, may break peptides at their ends (N and C termini) both within the nasal cavity and when they pass over the nasal epithelial barrier. Internal peptide bonds can also be broken by endopeptidases, such as serine and cysteine enzymes. This indicates that when proteins and peptides are delivered by the nose, they may be broken down by enzymes before they can enter the circulation or reach their intended locations. Therefore, to improve the efficacy of nasal medication administration for peptides and proteins, methods to shield these molecules from enzymatic degradation—such as enzyme inhibitors or modified formulations—are crucial [79,80,81,82]. Methods used to stop enzymatic breakdown, such as the use of protease and peptidase inhibitors. For example, trypsin inhibitors like leupeptin and aprotinin, as well as aminopeptidase inhibitors like comostate amylase, have been used to prevent the breakdown of chemicals like calcitonin. You can also take several absorption enhancers, such as fusidic acid and bile salts. Using inhibitors with trypsin-inhibiting qualities has been shown to improve salmon calcitonin's nasal absorption [83].

Thermoresponsive & ion-activated gels

In situ thermosensitive gel formulations are in a liquid state at ambient temperatures but transition to a gel form when they come into contact with the nasal mucosa, thereby prolonging the duration that the drug remains in the nasal cavity and enhancing its absorption [84,85,86]. In situ thermosensitive gels have emerged as a promising drug delivery technique for neuroprotection due to the advantage of localized and extended release of therapeutic medicines directly to the brain. Polymers like poloxamer, poly (N-isopropylacrylamide), polyethylene glycol, polyester, chitosan, etc. are typically used to create these thermosensitive gels [87,88,89]. At room temperature, these polymer solutions are liquids; but, when they approach body temperature, they transform into gels. This ensures that a medication depot may be built because it is easy to administer at the designated place. This targeted administration minimizes systemic exposure and potential side effects while optimizing the

concentration of the neuroprotective medication at the site of injury or illness [90].

Ion-activated systems (like gellan gum and sodium alginate), temperature-dependent systems (like Pluronic, Tetronics, and polymethacrylates), and pH-triggered systems (like Carbopol and cellulose acetate phthalate) are the three categories of in situ gelling systems. The primary benefit of in situ gels is that, in contrast to regular gels, they are easily administered with precise and repeatable dosages, have the advantage of being easily infused in liquid form, and can extend the formulation's residence time on the nasal cavity surface because of gelling [91,92,93].

Intranasal Nanomedicine in Specific CNS Disorders

Alzheimer's disease

Alzheimer's disease is a severe neurodegenerative disorder marked by impaired cognitive function, struggles with daily activities, and issues pertaining to learning, speech, and language [94,95]. The potential of polymeric and metal nanoparticles to treat Alzheimer's disease has drawn attention. These nanoparticles offer a number of benefits, including increased loading capacity, protection against degradation, improved stability, accurate targeting, lower dosage, and the possibility of improving affinity for A β proteins, which are a hallmark of AD [96]. Because of their controlled-release characteristics, biodegradable and biocompatible polymers such as chitosan, poly D, L-lactic-co-glycolic acid (PLGA), and polyvinyl alcohol (PVA) have been used for intranasal medication administration [97]. One potentially neuroprotective stilbenoid that may improve cognitive performance in Alzheimer's patients is resveratrol. However, its high metabolism and low bioavailability limit its therapeutic usefulness. Salem et al. created resveratrol-loaded transferosomes and nanoemulsions with gold nanoparticles (GNPs) for better distribution in order to get over these restrictions. To analyze spatial memory recovery, a variety of physicochemical characteristics were evaluated in addition to dynamic investigations including water maze testing. All treated groups showed gains in memory, according to the data, with the transferosome-GNP gel group matching the normal group. Interestingly, the transferosome-GNPs showed improved symptom relief and permeation (81.29 \pm 2.64%), along with a higher concentration of gold nanoparticles [98].

Parkinson's Disease

Parkinson's disease (PD) is a complex age-related neurodegenerative disorder that ranks second to Alzheimer's disease (AD) in prevalence. It is a multifactorial condition triggered by a variety of environmental and genetic factors, severely affecting patients' quality of life, and imposing a severe economic impact on society [99]. The creation of several nanocarrier systems, such as liposomes, nanogels, dendrimers, and solid lipid nanoparticles (SLNs), is one of the recent therapeutic uses of nanomedicine for the treatment of Parkinson's disease [100]. Liposomes and SLNs, which are frequently studied for the treatment of Parkinson's disease, make up the majority of lipid-based NPs. These NPs promote the transport of hydrophilic and hydrophobic medications across the blood-brain barrier, shield them from deterioration, and encapsulate them [101]. The medicine is released more easily into the target cells when the liposomes fuse with the cell membrane. SLNs, which are composed of solid lipids, provide a stable substitute for liposomes and can be used to efficiently distribute lipophilic medications [102]. Organic substances made of biocompatible and biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), are known as polymeric nanoparticles [103]. The capacity of these NPs to release medications in a regulated and sustained way is a significant benefit of utilizing them in the treatment of Parkinson's disease. This lowers the frequency of doses and facilitates patients' adherence to their treatment regimen. These polymeric NPs make up a significant class of NPs that are frequently utilized to treat Parkinson's disease [104].

Epilepsy

Antiepileptic medications must be administered via a variety of methods in order to treat both acute and chronic seizure disorders. Oral antiepileptic medications are frequently used for the long-term management of epilepsy [105]. When the oral route is not accessible or a prompt clinical response is needed, parenteral methods are utilized. Additionally, several medications can be given by the IN, buccal, or sublingual routes, particularly for therapy received outside of a hospital [106]. According to the Anderson research, the International League against Epilepsy's (ILAE) Task Force on Status Epilepticus consensus documents suggest rectal diazepam, buccal midazolam, or IN midazolam as out-of-hospital treatments for early seizures. Rather, Diastat® is the only rectal AED formulation that the FDA has

authorized for use at home in the United States [105]. AEDs can be encapsulated using nanomedicine to increase the therapeutic dosage at the brain, the target location, and lessen adverse effects because of the decreased biodistribution on peripheral organs. Using NPs to administer AEDs via IN administration is a very interesting area. Depending on certain factors, NPs may offer a great platform for the direct delivery of medications to the brain. Several authors have shown that the physico-chemical characteristics of NPs affect how they behave in the brain following IN delivery. It is well known that the 4S rules—size, shape, surface, and stability—determine how NPs are transported [107].

Depression & Anxiety

The most prevalent psychological problem and psychosocial ailment is depression. It is differentiated from depressing mental states and general sensations of despair [108]. Due to the numerous problems with antidepressant drugs, patients worldwide urgently require a new drug delivery system [109]. Drugs have been delivered to the brain using a variety of nanoparticulate therapeutic agent delivery methods [110]. Solid lipid nanoparticles (SLNs) are matrix nanoparticles that are dispersed in water or an aqueous surfactant solution. They are very biocompatible and tolerable, and they have exceptional physical stability without the usage of organic solvents during production. Because of their occlusive activity and mucosal adhesion, they also enable controlled drug release and extend the formulation's nasal retention time [111]. When compared to conventional zolmitriptan tablets, intranasal delivery of the solid lipid nanostructure via the olfactory pathway yielded a drug targeting potential of over 90% [112].

Drug delivery for anxiety disorders may be enhanced by nanoparticles, which may effectively cross the blood-brain barrier (BBB) and attach to certain brain receptors, such as GABAergic and serotonergic, that control anxiety or mood modulation [113]. As a controlled release system, they reduce the peaks and troughs that come with conventional dosage techniques, which can have negative consequences, particularly when it comes to managing anxiety [114]. Antianxiety medications are becoming more therapeutically effective because to the application of nanotechnology in drug delivery systems. Because they make it simple for benzodiazepines to penetrate the blood-brain barrier (BBB), nanoparticles can work wonders for them [115].

Because SSRIs are poorly soluble, using nanocarriers to boost absorption and deliver larger drug concentrations at the brain level may increase therapeutic benefits [116,117].

Brain tumors (Glioblastoma)

Drugs that selectively target tumor cells without damaging healthy organs have been developed, however getting these medications to brain tumors is still exceedingly challenging due to the blood- brain barrier's (BBB) resistance. The most frequent primary tumors in the human brain are malignant gliomas. Even after surgery followed by chemotherapy and radiation therapy, patients with glioblastoma (GBM), the most aggressive kind of malignant glioma, have a 5-year survival rate of fewer than 5% [118]. In order to maximize brain absorption and reduce systemic toxicity, traditional small molecule chemotherapeutics like paclitaxel and temozolomide have been investigated for intranasal delivery. The gold standard for treating glioblastoma, temozolomide, has problems with resistance and dose-limiting toxicity; intranasal administration can offer greater localized concentrations with less exposure to the surrounding environment. Similarly, when administered systemically, intranasal paclitaxel has demonstrated promise in preclinical models to reach therapeutic CNS levels that are otherwise limited by efflux transporters [119].

Migraine

The major symptom of migraine is a severe throbbing and pulsing pain around the head; its secondary symptoms, which are nausea, vomiting, and photophobia, are also quite prevalent [120,121]. Nasal medication administration is a potential non-invasive option since it decreases GI-related adverse effects, avoids the breakdown of labile medicines (such peptides and proteins) in the GI tract, and has a quick commencement of action [122]. Many anti-migraine medications, including sumatriptan, zolmitriptan, and others, have low bioavailability when administered intranasally. For this reason, polymeric nanoformulations of these medications were used to generate high bioavailability and quick absorption in migraine attacks, as opposed to oral tablets [123,124]. Intranasal nanoemulsion delivery devices for rizatriptan were studied for antimigraine treatment in order to improve its bioavailability and brain targeting [125].

Multiple sclerosis

The central nervous system (CNS) is affected by the demyelinating inflammatory and neurodegenerative illness known as multiple sclerosis (MS). Optic neuritis linked to irreversible vision loss due to retinal ganglion cell (RGC) injury is a common symptom [126]. Intranasal cell administration in animal models of multiple sclerosis has been employed in a small number of studies to date; most of them have used the experimental autoimmune encephalomyelitis (EAE) model. Fransson et al. (2014) used modified MSCs that expressed a particular myelin

oligodendrocyte glycoprotein receptor. In EAE mice, cells were given intranasally, reaching the cerebellum, entorhinal cortex, and olfactory bulb. Clinical improvement and decreased inflammation and demyelination were the outcomes of this [127]. One of the earliest studies to employ this cell lineage for intranasal administration was Gómez-Pinedo et al.'s use of the intranasal route to deliver oligodendrocyte- lineage cells, which reached the olfactory bulb and migrated to regions with quiescent endogenous OPCs (fimbria, corpus callosum, and septum) [128].

Therapeutic Agents Delivered via Intranasal Nanomedicine

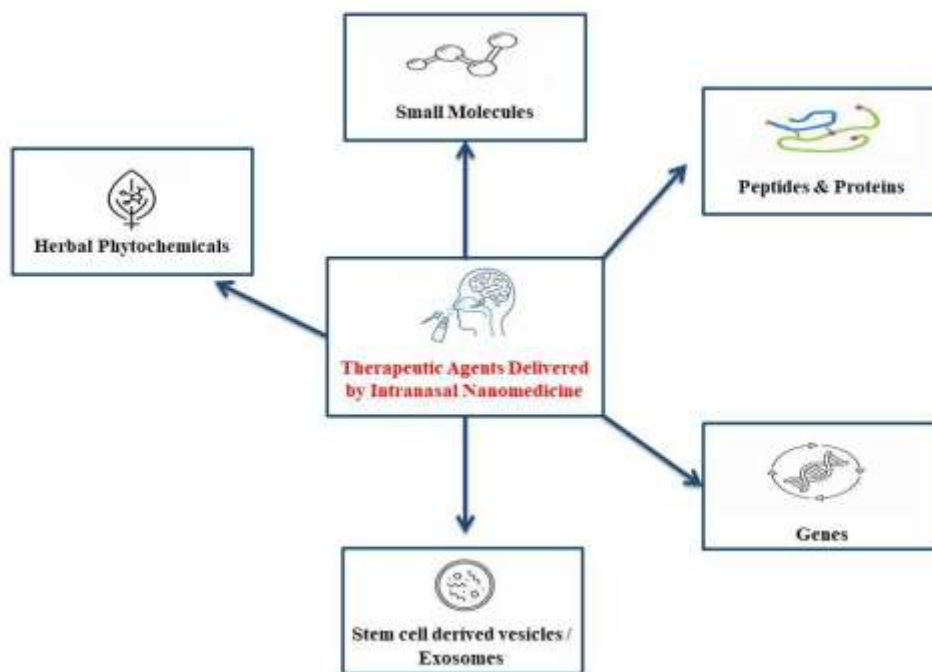


Figure 3 : Therapeutic Agents Delivered by Intranasal Nanomedicine

Small molecules

The tiny molecular weight and excellent oral absorption of small molecule medicines make them popular in clinical practice. Many studies have been conducted on the intranasal administration of small molecule medications, especially for the treatment of central nervous system disorders. For instance, it has been demonstrated that intranasal administration of galantamine, 9-cis retinoic acid, lacosamide, or isocyanomethane is useful in treating AD and epilepsy [129,130,131,132]. Benefits of intranasal administration include quick onset, simplicity of

usage, and good patient tolerance, particularly for elderly patients who have trouble swallowing oral medications [133]. Intranasal delivery of morphine or midazolam can be used to treat pain and agitation in palliative care and community hospice therapy. It is easy to administer and is a great option for patients who have trouble swallowing or are afraid of needles [134].

Peptides & proteins

Cyclodextrins have shown to be one of the most effective methods for directing peptides to different areas. In order to improve the intranasal

bioavailability of protein and peptide medications, cyclodextrins have long been utilized in nasal drug administration as adsorption-enhancing substances [135]. Additionally, recent research has shown that albumin may help target peptides to different parts of the brain. Albumin was able to modify leptin targeting following intranasal injection in a variety of ways to increase its effects in research involving leptin, a protein known to affect both appetite and cognition [136]. Insulin serves several vital purposes in the central nervous system. This involves improving memory, influencing how the hippocampus and other parts of the brain use glucose, and promoting synaptogenesis and synaptic remodelling [137]. Since boosting brain insulin signaling enhances memory functions in cognitively healthy adults and has neuroprotective qualities, it has been postulated that raising brain insulin concentrations in AD patients might prevent or halt the disease's progression [138].

Genes

Therapeutics based on nucleic acids have the ability to alter gene expression at both the transcriptional and post-transcriptional levels. These include of nucleosides, DNA aptamers, DNA plasmids, oligonucleotides, antisense RNA, microRNA, small interfering RNAs, and other similar compounds [139]. Important processes in gene delivery include viral transduction and non-viral transfection, which involve the introduction of foreign nucleic acids into host cells for the purpose of achieving gene expression, deletion, or silence. Despite its potential, nasal administration is extremely difficult because of the nasal cavity's unique anatomical and physiological characteristics. Since successful transfection or transduction entails not only getting genetic material to the intended location but also effectively internalizing and expressing it within cells of the nasal epithelium, olfactory region, or even in CNS-related pathways via the olfactory and trigeminal nerves, it is crucial for attaining successful therapeutic outcomes. In order to overcome these restrictions, gene delivery vectors must be carefully designed. Unwanted transduction and transduction may occur along the nasal route, and pathological abnormalities in the nasal cavity might affect the effectiveness of administration [73,140,141].

Stem cell derived vesicles / exosomes

A significant amount of study has been focused on clarifying the function of exosomes as a vital stem cell therapy method in recent years.

DNA, mRNA, microRNA (miRNA), and proteins are among the many substances found in exosomes, also known as extracellular vesicles, which are nano-sized vesicles with a diameter of 40–200 nm and are made of a double lipid-layer membrane [142]. Exosomes' tiny size allows the olfactory and trigeminal nerves to efficiently absorb them, allowing them to pass across the blood-brain barrier and transmit axonically to brain cells [143].

Herbal phytochemicals

Phytochemicals are medicinal substances that are produced by plants and have antibacterial, neuroprotective, anti-inflammatory, and antioxidant properties [144]. The nasal route of medication delivery has become a new and efficient way to get beyond the drawbacks of conventional delivery methods. While the olfactory and trigeminal neuronal pathways offer a direct physical link to the brain, avoiding the blood–brain barrier (BBB), a significant barrier for CNS medication delivery, the nasal mucosa is extensively vascularized and permits fast systemic absorption [145,146]. One appealing non-invasive method of delivering phytochemicals and medicinal substances to the central nervous system (CNS) is through the nose. Nasal medication administration avoids the blood-brain barrier (BBB) and offers a direct and efficient path to the tissues of the brain cells because of the unique physical connection between the nasal mucosa, olfactory bulb, and brain. Recent approaches based on nanotechnology, such as liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and nanoemulsions, have significantly increased the pharmacological potential of natural substances in the treatment of systemic and neurodegradative illnesses [147,148].

II. CHALLENGES AND LIMITATIONS

To guarantee efficient CNS administration, formulation development is still a significant challenge that necessitates meticulous optimization of drug stability, controlled release kinetics, mucoadhesive qualities, and targeting capabilities [149]. Studies on non-human primates have shown that intranasal medication administration has a good safety record. Increasing exposure to the brain while lowering systemic adverse effects is one of its specialties. But prolonged use over time may cause mucosal irritation and possibly olfactory impairment, therefore further research into its long-term safety in people is required [150]. Neuronal inflammation,

degeneration, or altered signaling may result from drugs and excipients used in formulations, such as permeation enhancers, surfactants, or cationic polymers like chitosan, that compromise the integrity of the nasal epithelium. Trigeminal fibers and olfactory neurons may experience oxidative stress or excitotoxicity as a result of high-dose or repeated exposure to neuroactive substances. Despite the increased bioavailability of various delivery technologies, nothing is known about how safe they are for neural structures [30,151]. In conclusion, despite intranasal nanomedicine's promising potential for targeted central nervous system therapy, a number of obstacles still prevent its widespread clinical application. To balance therapeutic efficacy with minimal toxicity and guarantee dependable patient outcomes in future applications, standardization of formulations, thorough long-term safety evaluations, and a deeper comprehension of nose-to-brain transport mechanisms are crucial.

III. FUTURE PERSPECTIVES

We may infer from the research conducted in recent years that nanotechnology is effectively gaining more attention. For the administration of CNS treatments, a variety of nanocarriers have been investigated, including polymeric nanoparticles, solid lipid nanoparticles, liposomes, micelles, dendrimers, nanogels, nanoemulsions, and nanosuspensions [152]. Large-scale production is a major difficulty in addition to cost. Certain NP synthesis techniques, such as emulsification, solvent evaporation, and nanoprecipitation, are best suited for laboratory or pilot scale production and might not work well in industrial settings. Scaling up makes it harder to maintain consistency in drug encapsulation, morphology, and particle size, which might jeopardize batch-to-batch consistency, which is essential for regulatory clearance. For intranasal formulations, reproducibility and stability are particularly important since differences in particle properties might impact mucosal penetration, residence duration, and ultimately the effectiveness of brain targeting [153]. In order to move intranasal nanomedicine from research to clinical practice, it will be essential to integrate quality-by-design techniques, advanced manufacturing technologies, and regulatory harmonization. Working together, academia and industry could support more individualized CNS therapies with improved therapeutic precision, increase scalable production, and strengthen formulation robustness.

IV. CONCLUSION

Due in large part to the blood-brain barrier's (BBB) restrictive nature, which keeps the great majority of medications from entering the brain, treating disorders of the central nervous system (CNS) is still one of the most difficult problems in modern medicine. Intranasal nanomedicine, as discussed in this review, offers a revolutionary way to get around this problem by using the trigeminal and olfactory nerve pathways to deliver drugs directly from the nose to the brain. By potentially lowering peripheral toxicity and increasing drug concentration at the target site, this non-invasive method provides a substantial advantage over systemic administration. In order to overcome the physiological constraints of the nasal cavity, such as quick mucociliary clearance and enzymatic degradation, nanocarriers such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), dendrimers, and in situ gels have evolved. These formulations can greatly increase residence time and promote mucosal penetration by using stimuli-responsive systems and mucoadhesive polymers like chitosan. Additionally, because of these nanoplateforms' versatility, a broad range of therapeutic agents, from sensitive macromolecules like proteins, peptides, and genetic material to small hydrophobic molecules and herbal phytochemicals, can be encapsulated and delivered.

There are obstacles in the way of moving from the bench to the bedside, despite the encouraging preclinical data for a number of conditions, including glioblastoma, Parkinson's disease, Alzheimer's disease, and epilepsy. Thorough consideration must be given to concerns about the long-term safety of nasal excipients, possible irritation of the mucosa, and the reproducibility of large-scale manufacturing. Standardization of formulation technologies and ongoing industry-research cooperation are ultimately necessary for intranasal nanomedicine to succeed in the future and guarantee that these cutting-edge delivery systems are both scalable and clinically safe for broad patient use.

REFERENCES

- [1]. Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. *Recent Pat Drug Deliv Formul.* 2012;6(1):2-18.
- [2]. Hyman S, Chisholm D, Kessler R, Petal V, Whiteford H. Mental disorders. In: Jamison DT, Breman JG, Measham AR,

- Alleyne G, Claeson M, Evans DB, et al., editors. Disease control priorities in developing countries. New York: Oxford University Press; 2006. p. 605-25.
- [3]. Dinunzio JC, Williams RO. CNS disorders—current treatment options and the prospects for advanced therapies. *Drug Dev Ind Pharm.* 2008;34(11):1141-1167.
- [4]. US Food and Drug Administration. FDA grants accelerated approval for Alzheimer's drug [Internet]. 2021 [cited 2026 Feb 11]. Available from: <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug>
- [5]. Steinmetz JD, Seeher KM, Schiess N, et al.; GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* 2024;23(4):344-381. doi:10.1016/S1474-4422(24)00038-3.
- [6]. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys 1990–2014: a systematic review and meta-analysis. *Drug Alcohol Rev.* 2015;154:1–13.
- [7]. United Nations Office on Drugs and Crime (UNODC). Comorbidities in drug use disorders. Vienna (Austria): UNODC; 2022.
- [8]. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater.* 2021;6:1078–94.
- [9]. Torchilin VP. Multifunctional nanocarriers. *Adv Drug Deliv Rev.* 2006;58:1532–55.
- [10]. Gatto MS, Johnson MP, Najahi-Missaoui W. Targeted liposomal drug delivery: overview of the current applications and challenges. *Life (Basel).* 2024;14:672.
- [11]. Xu Y, et al. Surface modification of lipid-based nanoparticles. *ACS Nano.* 2022;16:7168–96.
- [12]. Li Z, et al. Applications of surface modification technologies in nanomedicine for deep tumor penetration. *Adv Sci.* 2021;8:2002589.
- [13]. Varsha Z, Gite VZ, Ghume VK, Kachave RN. Brain targeted drug delivery system. *World J Pharm Med Res.* 2020;6(11):45–57.
- [14]. Shinde SC, Mahale NB, Chaudhari SR, Thorat RS. Recent advances in brain targeted drug delivery system: a review. *World J Pharm Res.* 2015;4(5):542–9.
- [15]. Gotovac K, Hajnšek S, Pašić MB, Pivac N, Borovečki F. Personalized medicine in neurodegenerative diseases: how far away? *Mol Diagn Ther.* 2014;18(1):17–24. doi:10.1007/s40291-013-0058-z.
- [16]. Henrich-Noack P, et al. The blood–brain barrier and beyond: nano-based neuropharmacology and the role of extracellular matrix. *Nanomedicine.* 2019;17:359–79.
- [17]. Illum L. Transport of drugs from the nasal cavity to the central nervous system. *Eur J Pharm Sci.* 2000;11:1–18. doi:10.1016/S0928-0987(00)00087-7.
- [18]. Thorne RG, Lochhead JJ. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev.* 2011;64:614–28. doi:10.1016/j.addr.2011.11.002.
- [19]. Wong HL, Wu XY, Bendayan R. Nanotechnological advances for the delivery of CNS therapeutics. *Adv Drug Deliv Rev.* 2012;64(7):686–700. doi:10.1016/j.addr.2011.10.007.
- [20]. Hwang JY, Shin US, Jang WC, Hyun JK, Wall IB, Kim HW. Biofunctionalized carbon nanotubes in neural regeneration: a mini-review. *Nanoscale.* 2013;5(2):487–97. doi:10.1039/c2nr31581e.
- [21]. 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;10:957–72. doi:10.1517/17425247.2013.790887.
- [22]. 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;5:709–33. doi:10.4155/tde.14.41.
- [23]. Khunt D, Misra M. 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. Cambridge (MA): Academic Press; 2021. p. 3–14.

- [24]. 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*. Cham (Switzerland): Springer International Publishing; 2023. p. 1–13.
- [25]. Chapman CD, Frey WH 2nd, Craft S, et al. Intranasal treatment of central nervous system dysfunction in humans. *Pharm Res*. 2012;30(10):2475–84.
- [26]. Bastir M, Rosas A, Gunz P, et al. Evolution of the base of the brain in highly encephalized human species. *Nat Commun*. 2011;2:588.
- [27]. Agrawal M, Saraf S, Saraf S, Antimisiaris S, Chougule M, Shoyele S, Alexander A. 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. doi:10.1016/j.jconrel.2018.05.011.
- [28]. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurason S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res Bull*. 2018;143:155–70. doi:10.1016/j.brainresbull.2018.10.009.
- [29]. Schwarz B, Merkel OM. Nose-to-brain delivery of biologics. *Ther Deliv*. 2019;10:207–10. doi:10.4155/tde-2019-0013.
- [30]. Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc LJ, et al. Intranasal drug delivery: an efficient and non-invasive route for systemic administration. *Pharmacol Ther*. 2012;134:366–79. doi:10.1016/j.pharmthera.2012.03.003.
- [31]. Warnken ZN, Smyth HDC, Watts AB, Weitman SD, Kuhn JG, Williams RO. Formulation and device design to increase nose-to-brain drug delivery. *J Drug Deliv Sci Technol*. 2016;3:213–22.
- [32]. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics*. 2018;10(3):116.
- [33]. Bhise S, Yadav A, Avachat A, Malayandi R. Bioavailability of intranasal drug delivery system. *Asian J Pharm*. 2018;2:201.
- [34]. Ruigrok MJ, De Lange EC. Emerging insights for translational pharmacokinetic and pharmacokinetic- pharmacodynamic studies: towards prediction of nose-to-brain transport in humans. *AAPS J*. 2015;17(3):493–505.
- [35]. Sakane T, Akizuki M, Yoshida M, Yamashita S, Nadai T, Hashida M, Sezaki H. Transport of cephalexin to the cerebrospinal fluid directly from the nasal cavity. *J Pharm Pharmacol*. 1991;43:449–51. doi:10.1111/j.2042-7158.1991.tb03510.x.
- [36]. Awad R, Avital A, Sosnik A. Polymeric nanocarriers for nose-to-brain drug delivery in neurodegenerative diseases and neurodevelopmental disorders. *Acta Pharm Sin B*. 2023;13(5):1866–86. doi:10.1016/j.apsb.2022.07.003.
- [37]. Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. *Methods Mol Biol*. 2010;624:25–37. doi:10.1007/978-1-60761-609-2_3.
- [38]. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine*. 2008;3:133.
- [39]. Zorkina Y, Abramova O, Ushakova V, Morozova A, Zubkov E, Valikhov M, et al. Nanocarrier drug delivery systems for the treatment of neuropsychiatric disorders: advantages and limitations. *Molecules*. 2020;25:5294. doi:10.3390/molecules25225294.
- [40]. Alexander A, Saraf S. Nose-to-brain drug delivery approach: a key to easily accessing the brain for the treatment of Alzheimer's disease. *Neural Regen Res*. 2018;13:2102–4. doi:10.4103/1673-5374.241458.
- [41]. Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric nanoparticles for drug delivery. *Methods Mol Biol*. 2010;624:163–75. doi:10.1007/978-1-60761-609-2_11.
- [42]. Spandana KA, Bhaskaran M, Karri VR, Natarajan J. A comprehensive review of nano drug delivery system in the treatment of CNS disorders. *J Drug Deliv Sci Technol*. 2020;57:101628. doi:10.1016/j.jddst.2020.101628.
- [43]. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable

- controlled drug delivery carrier. *Polymers*. 2011;3:1377–97. doi:10.3390/polym3031377.
- [44]. Emad NA, Ahmed B, Alhalmi A, Alzobaidi N, Al-Kubati SS. Recent progress in nanocarriers for direct nose-to-brain drug delivery. *J Drug Deliv Sci Technol*. 2021;64:102642. doi:10.1016/j.jddst.2021.102642.
- [45]. Vieira DB, Gamarra LF. Getting into the brain: liposome-based strategies for effective drug delivery across the blood–brain barrier. *Int J Nanomedicine*. 2016;11:5381–414. doi:10.2147/IJN.S117210.
- [46]. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to- brain delivery of pharmaceuticals. *Eur J Pharm Biopharm*. 2018;128:337–62. doi:10.1016/j.ejpb.2018.05.009.
- [47]. Lee DV, Minko T. Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood– brain barrier. *Pharmaceutics*. 2021;13(12):2049. doi:10.3390/pharmaceutics13122049.
- [48]. Ahmad E, Feng YH, Qi JP, Fan W, Ma Y, He H, et al. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. *Nanoscale*. 2017;9(3):1174–83. doi:10.1039/c6nr07581a.
- [49]. Nguyen TT, Nguyen TTD, Tran NMA, Van Vo G. Lipid-based nanocarriers via nose-to-brain pathway for central nervous system disorders. *Neurochem Res*. 2022;47(3):552–73. doi:10.1007/s11064-021-03488-7.
- [50]. Alam MI, Baboota S, Ahuja A, Ali M, Ali J, Sahni JK, et al. Pharmacoscintigraphic evaluation of potential of lipid nanocarriers for nose-to-brain delivery of antidepressant drug. *Int J Pharm*. 2014;470(1–2):99–106. doi:10.1016/j.ijpharm.2014.05.004.
- [51]. Du X, Shi B, Liang J, Bi J, Dai S, Qiao SZ. Developing functionalized dendrimer-like silica nanoparticles with hierarchical pores as advanced delivery nanocarriers. *Adv Mater*. 2013;25:5981–5. doi:10.1002/adma.201302189.
- [52]. Esfand R, Tomalia DA. Poly(amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. *Drug Discov Today*. 2001;6:427–36. doi:10.1016/S1359-6446(01)01757-3.
- [53]. Gao K, Jiang X. Influence of particle size on transport of methotrexate across blood–brain barrier by polysorbate 80-coated polybutylcyanoacrylate nanoparticles. *Int J Pharm*. 2006;310:213–9. doi:10.1016/j.ijpharm.2005.11.040.
- [54]. Hanada S, Fujioka K, Inoue Y, Kanaya F, Manome Y, Yamamoto K. Cell-based in vitro blood–brain barrier model can rapidly evaluate nanoparticles’ brain permeability in association with particle size and surface modification. *Int J Mol Sci*. 2014;15:1812–25. doi:10.3390/ijms15021812.
- [55]. Zheng S, Bai YY, Changyi Y, Gao X, Zhang W, Wang Y, Zhou L, Ju S, Li C. Multimodal nanoprobe evaluating physiological pore size of brain vasculatures in ischemic stroke models. *Adv Healthc Mater*. 2014;3:1909–18. doi:10.1002/adhm.201400159.
- [56]. Kannan S, Dai H, Navath RS, Balakrishnan B, Jyoti A, Janisse J, Romero R, Kannan RM. Dendrimer-based postnatal therapy for neuroinflammation and cerebral palsy in a rabbit model. *Sci Transl Med*. 2012;4:130ra46. doi:10.1126/scitranslmed.3003162.
- [57]. Sabale AS, Kulkarni AD, Sabale AS. Nasal in situ gel: novel approach for nasal drug delivery. *J Drug Deliv Ther*. 2020;10(2 Suppl):183–97. doi:10.22270/jddt.v10i2-s.4029.
- [58]. Rajput AP, Butani SB. Resveratrol anchored nanostructured lipid carrier loaded in situ gel via nasal route: formulation, optimization and in vivo characterization. *J Drug Deliv Sci Technol*. 2019;51:214–23. doi:10.1016/j.jddst.2019.01.040.
- [59]. Adnet T, Groo AC, Picard C, et al. Pharmacotechnical development of a nasal drug delivery composite nanosystem intended for Alzheimer’s disease treatment. *Pharmaceutics*. 2020;12(3):251. doi:10.3390/pharmaceutics12030251.
- [60]. Neamtu I, Rusu AG, Diaconu A, Nita LE, Chiriac AP. Basic concepts and recent advances in nanogels as carriers for medical applications. *Drug Deliv*. 2017;24:539–57.

- [61]. Tahara Y, Akiyoshi K. Current advances in self-assembled nanogel delivery systems for immunotherapy. *Adv Drug Deliv Rev.* 2015;95:65–76.
- [62]. Hendrickson GR, Lyon LA. Microgel translocation through pores under confinement. *Angew Chem Int Ed.* 2010;49:2193–7.
- [63]. Zhang L, Cao Z, Li Y, Ella-Menye JR, Bai T, Jiang SY. Softer zwitterionic nanogels for longer circulation and lower splenic accumulation. *ACS Nano.* 2012;6:6681–6.
- [64]. Porfiryeva NN, Semina II, Salakhov IA, Moustafine RI, Khutoryanskiy VV. Mucoadhesive and mucus- penetrating interpolyelectrolyte complexes for nose-to-brain drug delivery. *Nanomed Nanotechnol Biol Med.* 2021;37:102432. doi:10.1016/j.nano.2021.102432.
- [65]. Bruinsmann FA, Pigana S, Aguirre T, Souto GD, Pereira GG, Bianchera A, Fasiolo LT, Colombo G, Marques M, Pohlmann AR, Guterres SS, Sonvico F. Chitosan-coated nanoparticles: effect of chitosan molecular weight on nasal transmucosal delivery. *Pharmaceutics.* 2019;11:299.
- [66]. Snyers D, Tribolet S, Rigo V. Intranasal analgesia for infants in the neonatal intensive care unit: a systematic review. *Neonatology.* 2022;119:273–84. doi:10.1159/000521949.
- [67]. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. *Drug Deliv Transl Res.* 2021;12:735–57. doi:10.1007/s13346-020-00891-5.
- [68]. Gotoh S, Kawabori M, Fujimura M. Intranasal administration of stem cell-derived exosomes for central nervous system diseases. *Neural Regen Res.* 2024;19:1249–55. doi:10.4103/1673-5374.385875.
- [69]. Lochhead JJ, Davis TP. Perivascular and perineural pathways involved in brain delivery and distribution of drugs after intranasal administration. *Pharmaceutics.* 2019;11:598. doi:10.3390/pharmaceutics11110598.
- [70]. Gandhi S, Shastri DH, Shah J, Nair AB, Jacob S. Nasal delivery to the brain: harnessing nanoparticles for effective drug transport. *Pharmaceutics.* 2024;16:481. doi:10.3390/pharmaceutics16040481.
- [71]. Zha S, Wong KL, All AH. Intranasal delivery of functionalized polymeric nanomaterials to the brain. *Adv Healthc Mater.* 2022;11:2102610. doi:10.1002/adhm.202102610.
- [72]. Mohammed MA, Syeda JTM, Wasan KM, Wasan EK. An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. *Pharmaceutics.* 2017;9:53. doi:10.3390/pharmaceutics9040053.
- [73]. Sun B, Zhang M, Shen J, He Z, Fatehi P, Ni Y. Applications of cellulose-based materials in sustained drug delivery systems. *Curr Med Chem.* 2019;26:2485–501. doi:10.2174/0929867324666170705143308.
- [74]. Amin MK, Boateng JS. Comparison and process optimization of PLGA, chitosan and silica nanoparticles for potential oral vaccine delivery. *Ther Deliv.* 2019;10:493–514. doi:10.4155/tde-2019-0038.
- [75]. Muzzarelli RA. Human enzymatic activities related to the therapeutic administration of chitin derivatives. *Cell Mol Life Sci.* 1997;53:131–40. doi:10.1007/PL00000584.
- [76]. Deacon MP, McGurk S, Roberts CJ, Williams PM, Tendler SJ, Davies MC, Davis SS, Harding SE. Atomic force microscopy of gastric mucin and chitosan mucoadhesive systems. *Biochem J.* 2000;348:557–63. doi:10.1042/bj3480557.
- [77]. Kamei N, Okada N, Ikeda T, Choi H, Fujiwara Y, Okumura H, et al. Effective nose-to-brain delivery of exendin-4 via coadministration with cell-penetrating peptides for improving progressive cognitive dysfunction. *Sci Rep.* 2018;8(1):1–4.
- [78]. Hinchcliffe M, Illum L. Intranasal insulin delivery and therapy. *Adv Drug Deliv Rev.* 1999;35:199–234.
- [79]. Krishnarajan D, Tamilselvan A, Abraham S, Mathew RJ, Ramya S, Raja KR. New approaches of nasal drug delivery system. *Pharmacophore.* 2016;7(4):242–64.
- [80]. Mittal S, Jobin J, Kawale S. Review on nasal drug delivery system. *World J Pharm Sci.* 2014;2(9):1058–70.
- [81]. Jadhav KR, Gambhire MN, Shaikh IM, Kadam VJ, Pisal SS. Nasal drug delivery system—factors affecting and

- applications. *Curr Drug Ther.* 2007;2(1):27–38. doi:10.2174/157488507779422374.
- [82]. Morimoto K, Miyazaki M, Kakemi M. Effects of proteolytic enzyme inhibitors on nasal absorption of salmon calcitonin in rats. *Int J Pharm.* 1995;113(1):1–8. doi:10.1016/0378-5173(94)00158-2.
- [83]. Shao J. Nasal delivery of proteins and peptides. *Glob J Pharm Pharm Sci.* 2017;1(4). doi:10.19080/GJPPS.2017.01.555569.
- [84]. Kazi-Chishti M, Shaikh J, Chishti N, Dehghan MH. Nasal mucoadhesive in situ gelling liquid crystalline fluid precursor system of polyene antibiotic for potential treatment of localized sinuses aspergillosis post COVID infection. *J Dispers Sci Technol.* 2024;45:1373–91.
- [85]. Anjali S, Abhijeet K, Ajay S, Kulkarni A. Nasal in situ gel: novel approach for nasal drug delivery. *J Drug Deliv Ther.* 2020;10:183–97.
- [86]. Qian L, Cook MT, Dreiss CA. In situ gels for nasal delivery: formulation, characterization and applications. *Macromol Mater Eng.* 2025;2400356.
- [87]. Wu Z, Wu W, Zhang C, Zhang W, Li Y, Ding T, Fang Z, Jing J, He X, Huang F. Enhanced diabetic foot ulcer treatment with a chitosan-based thermosensitive hydrogel loaded self-assembled multifunctional nanoparticles for antibacterial and angiogenic effects. *Carbohydr Polym.* 2025;347:122740.
- [88]. Anggela MR, Cheng H, Lin C. Thermosensitive hydrogels as targeted and controlled drug delivery systems: potential applications in transplantation. *Macromol Biosci.* 2024;24:2400064.
- [89]. Zhang K, Xue K, Loh XJ. Thermo-responsive hydrogels: from recent progress to biomedical applications. *Gels.* 2021;7:77.
- [90]. Singh M, Kumar S, Vinayagam R, Samivel R. Thermosensitive mucoadhesive intranasal in situ gel of risperidone for nose-to-brain targeting: physicochemical and pharmacokinetics study. *Pharmaceuticals (Basel).* 2025;18(6):871. doi:10.3390/ph18060871.
- [91]. Gibaldi M, Perrier D, editors. *Pharmacokinetics.* 2nd ed. Boca Raton (FL): CRC Press; 1982. doi:10.1201/b14095.
- [92]. HB N, Bakliwal S, Pawar S. In-situ gel: new trends in controlled and sustained drug delivery system. *Int J PharmTech Res.* 2010;2(2):1398–408.
- [93]. Zaki NM, Awad GA, Mortada ND, Abd ElHady SS. Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. *Eur J Pharm Sci.* 2007;32(4–5):296–307.
- [94]. Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer’s disease. *Mol Neurodegener.* 2020;15:40. doi:10.1186/s13024-020-00391-7.
- [95]. Vinicius M, De Mello C, Vieira L, de Souza LC, Gomes K, Carvalho M. Alzheimer’s disease: risk factors and potentially protective measures. *J Biomed Sci.* 2019;26:33. doi:10.1186/s12929-019-0524-y.
- [96]. Modi G, Pillay V, Choonara YE. Advances in the treatment of neurodegenerative disorders employing nanotechnology. *Ann N Y Acad Sci.* 2010;1184:154–72. doi:10.1111/j.1749-6632.2009.05108.x.
- [97]. Raj R, Wairkar S, Sridhar V, Gaud R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose- to-brain delivery: development, characterization and in vivo anti-Parkinson activity. *Int J Biol Macromol.* 2018;109:27–35. doi:10.1016/j.ijbiomac.2017.12.056.
- [98]. Salem HF, Kharshoum RM, Abou-Taleb HA, Naguib DM. Brain targeting of resveratrol through intranasal lipid vesicles labelled with gold nanoparticles: in vivo evaluation and bioaccumulation investigation using computed tomography and histopathological examination. *J Drug Target.* 2019;27:1127–34. doi:10.1080/1061186X.2019.1608553.
- [99]. Khatri DK, Preeti K, Tonape S, Bhattacharjee S, Patel M, Shah S, Singh PK, Srivastava S, Gugulothu D, Vora L, Singh SB. Nanotechnological advances for nose-to-brain delivery of therapeutics to improve Parkinson therapy. *Curr Neuropharmacol.* 2023;21(3):493–516.

- [100]. Grisold W. The expanding burden of neurological disorders. *Lancet Neurol.* 2024; 23:326–7. doi:10.1016/S1474-4422(24)00086-3.
- [101]. Jana M, Biswas UK, Patra CS, Debnath B, Sharma S, Naskar S. Solid lipid nanoparticles: a review of their biomedical applications and preparation. *Pharm Nanotechnol.* 2024; 12:1–17. doi:10.2174/0122117385312175240502100018.
- [102]. Sujeevan O. Lipid-based nanoparticles and their recent advances. *GSC Adv Res Rev.* 2024; 18:182–8. doi:10.30574/gscarr.2024.18.3.0096.
- [103]. Bhardwaj H, Jangde RK. Current updated review on preparation of polymeric nanoparticles for drug delivery and biomedical applications. *Next Nanotechnol.* 2023; 2:100013. doi:10.1016/j.nxnano.2023.100013.
- [104]. Geszke-Moritz M, Moritz M. Biodegradable polymeric nanoparticle-based drug delivery systems: comprehensive overview, perspectives and challenges. *Polymers.* 2024; 16:2536. doi:10.3390/polym16172536.
- [105]. Anderson GD, Saneto RP. Current oral and non-oral routes of antiepileptic drug delivery. *Adv Drug Deliv Rev.* 2012; 64:911–18.
- [106]. Ulgey A, Aksu R, Bicer C. Nasal and buccal treatment of midazolam in epileptic seizures in pediatrics. *Clin Med Insights Pediatr.* 2012; 6:51–60.
- [107]. Carbone C, Manno D, Serra A, Musumeci T, Pepe V, Tisserand C, Puglisi G. Innovative hybrid vs polymeric nanocapsules: the influence of the cationic lipid coating on the “4S”. *Colloids Surf B Biointerfaces.* 2016; 141:450–7.
- [108]. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health surveys. *Psychol Med.* 2018;48(9):1560–71. doi:10.1017/S0033291717003336.
- [109]. Cuijpers P, Stringaris A, Wolpert M. Treatment outcomes for depression: challenges and opportunities. *Lancet Psychiatry.* 2020;7(11):925-7. doi:10.1016/S2215-0366(20)30036-5.
- [110]. Nagpal K, Singh SK, Mishra DN. Drug targeting to brain: a systematic approach to study the factors, parameters and approaches for prediction of permeability of drugs across BBB. *Expert Opin Drug Deliv.* 2013;10(7):927-55. doi:10.1517/17425247.2013.762354.
- [111]. Prajapati JB, Patel GC. Nose to brain delivery of rotigotine loaded solid lipid nanoparticles: quality by design-based optimization and characterization. *J Drug Deliv Sci Technol.* 2021; 63:102377. doi:10.1016/j.jddst.2021.102377.
- [112]. Mostafa DAE, Khalifa MK, Gad SS. Zolmitriptan brain targeting via intranasal route using solid lipid nanoparticles for migraine therapy: formulation, characterization, in vitro and in vivo assessment. *Int J Appl Pharm.* 2020;12(2):86-93. doi:10.22159/ijap.2020v12i2.36812.
- [113]. McLoughlin CD, Nevins S, Stein JB, Khakbiz M, Lee KB. Overcoming the blood-brain barrier: multifunctional nanomaterial-based strategies for targeted drug delivery in neurological disorders. *Small Sci.* 2024; 12:2400232.
- [114]. Drishya S, Are RP, Hota P, Babu AR. Nanoparticles as drug delivery carrier—synthesis, functionalization and application. *Curr Pharm Des.* 2025; 31:244-60.
- [115]. Wilar G, Suhandi C, Wathoni N, Fukunaga K, Kawahata I. Nanoparticle-based drug delivery systems enhance treatment of cognitive defects. *Int J Nanomedicine.* 2024; 19:11357-78.
- [116]. Kisku A, Nishad A, Agrawal S, Paliwal R, Datusalia AK, Gupta G, et al. Recent developments in intranasal drug delivery of nanomedicines for the treatment of neuropsychiatric disorders. *Front Med.* 2024; 11:1463976. doi:10.3389/fmed.2024.1463976.
- [117]. Liang B, Zhou Y, Qin Y, Li X, Zhou S, Yuan K, et al. Research progress on using nanoparticles to enhance the efficacy of drug therapy for chronic mountain sickness. *Pharmaceutics.* 2024; 16:1375.
- [118]. Central Brain Tumor Registry of the United States (CBTRUS). Primary brain tumors in the United States: statistical report tables, 1998–2002. Chicago: CBTRUS; 2005. Available from: <http://www.cbtrus.org/2005-2006/tables/2006.table18-19.pdf>

- [119]. Duan M, Cao R, Yang Y, Chen X, Liu L, Ren B. Blood-brain barrier conquest in glioblastoma nanomedicine: strategies, clinical advances, and emerging challenges. *Cancers* (Basel). 2024;16(19):3300. doi:10.3390/cancers16193300.
- [120]. Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med*. 2002; 346:257-70.
- [121]. Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. Neurobiology of migraine. *Neuroscience*. 2009; 161:327-41.
- [122]. Kashyap K, Shukla R. Drug delivery and targeting to the brain through nasal route: mechanisms, applications and challenges. *Curr Drug Deliv*. 2019;16(10):887-901.
- [123]. Gulati N, Nagaich U, Saraf SA. Intranasal delivery of chitosan nanoparticles for migraine therapy. *Sci Pharm*. 2013;81(3):843-54.
- [124]. Sunena, Mishra DN, Singh SK, Kumar A. Development and characterization of zolmitriptan loaded thiolated chitosan nanoparticles for intranasal drug delivery. *Pharma Innov*. 2016; 5:19-23.
- [125]. Singh A, Ubrane R, Prasad P, Ramteke S. Preparation and characterization of rizatriptan benzoate loaded solid lipid nanoparticles for brain targeting. *Mater Today Proc*. 2015;2(9):4521-43.
- [126]. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. *JAMA*. 2021;325(8):765-79.
- [127]. Fransson M, Piras E, Wang H, Burman J, Duprez I, Harris RA, et al. Intranasal delivery of central nervous system-retargeted human mesenchymal stromal cells prolongs treatment efficacy of experimental autoimmune encephalomyelitis. *Immunology*. 2014;142(3):431-41.
- [128]. Gómez-Pinedo U, Matías-Guiu JA, Benito-Martín MS, Moreno-Jiménez L, Sanclemente-Alamán I, Selma-Calvo B, et al. Intranasal administration of undifferentiated oligodendrocyte lineage cells as a potential approach to deliver oligodendrocyte precursor cells into brain. *Int J Mol Sci*. 2021;22(19):10738.
- [129]. Nanaki SG, Spyrou K, Papadopoulos GC, Bekiari C, Veneti P, Karouta N, et al. Hierarchical porous carbon-PLLA and PLGA hybrid nanoparticles for intranasal delivery of galantamine for Alzheimer's disease therapy. *Pharmaceutics*. 2020; 12:227. doi:10.3390/pharmaceutics12030227.
- [130]. Gonçalves J, Alves G, Fonseca C, Carona A, Bicker J, Falcão A, Fortuna A. Is intranasal administration an opportunity for direct brain delivery of lacosamide? *Eur J Pharm Sci*. 2021; 157:105632. doi: 10.1016/j.ejps.2020.105632.
- [131]. Zolkowska D, Wu CY, Rogawski MA. Intranasal allopregnanolone confers rapid seizure protection: evidence for direct nose-to-brain delivery. *Neurotherapeutics*. 2021; 18:544-55. doi:10.1007/s13311-020-00985-5.
- [132]. Hong Z, Shuo L, Zhuo L, Shuo Y, Dandan L, Jiaolin Z, et al. Intranasal delivery of 9-cis retinoic acid reduces beta-amyloid deposition via inhibiting astrocyte-mediated inflammation. *Aging* (Albany NY). 2020; 12:5469-78. doi:10.18632/aging.102970.
- [133]. Ingielewicz A, Szymczak RK. Intranasal therapy in palliative care. *Pharmaceutics*. 2024; 16:519. doi:10.3390/pharmaceutics16040519.
- [134]. Nicholas TG, Husbands EL. Benefits of intranasal administration of diamorphine and midazolam in the management of patients receiving palliative care in the community: a case series. *J Pain Palliat Care Pharmacother*. 2022; 36:34-39. doi:10.1080/15360288.2022.2028955.
- [135]. Merkus FW, Verhoef JC, Marttin E, Romeijn SG, Van der Kuy PH, Hermens WA, Schipper NG. Cyclodextrins in nasal drug delivery. *Adv Drug Deliv Rev*. 1999;36(1):41-57.
- [136]. Falcone JA, Salameh TS, Yi X, Cordy BJ, Mortell WG, Kabanov AV, et al. Intranasal administration as a route for drug delivery to the brain: evidence for a unique pathway for albumin. *J Pharmacol Exp Ther*. 2014;351(1):54-60.
- [137]. Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. *Pharmacol Ther*. 2012;136(1):82-93.
- [138]. Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology*. 2004;29(10):1326-34.

- [139]. Kulkarni JA, Witzigmann D, Thomson SB, Chen S, Leavitt BR, Cullis PR, van der Meel R. The current landscape of nucleic acid therapeutics. *Nat Nanotechnol.* 2021; 16:630-43. doi:10.1038/s41565-021-00898-0.
- [140]. Shah P, Lalan M, Barve K. Intranasal delivery: an attractive route for the administration of nucleic acid- based therapeutics for CNS disorders. *Front Pharmacol.* 2022; 13:974666. doi:10.3389/fphar.2022.974666.
- [141]. Ye D, Chukwu C, Yang Y, Hu Z, Chen H. Adeno-associated virus vector delivery to the brain: technology advancements and clinical applications. *Adv Drug Deliv Rev.* 2024; 211:115363. doi: 10.1016/j.addr.2024.115363.
- [142]. Kosaka N, Iguchi H, Ochiya T. Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. *Cancer Sci.* 2010;101(10):2087-92.
- [143]. Gotoh S, Kawabori M, Fujimura M. Intranasal administration of stem cell-derived exosomes for central nervous system diseases. *Neural Regen Res.* 2024;19(6):1249-55. doi:10.4103/1673-5374.385875.
- [144]. Godos J, Carota G, Caruso G, et al. Molecular mechanisms underlying the neuroprotective effects of polyphenols: implications for cognitive function. *EXCLI J.* 2025; 24:1262-94. doi:10.17179/excli2025-8779.
- [145]. Rajput A, Pingale P, Dhapte-Pawar V. Nasal delivery of neurotherapeutics via nanocarriers: facets, aspects, and prospects. *Front Pharmacol.* 2022; 13:979682. doi:10.3389/fphar.2022.979682.
- [146]. Bicker J, Fortuna A, Alves G. Nose-to-brain delivery of natural compounds for the treatment of central nervous system disorders. *Curr Pharm Des.* 2020;26(26):2967-83. doi:10.2174/1381612826666200115101544.
- [147]. Ashfaq R, Rasul A, Asghar S, Kovács A. Lipid nanoparticles: an effective tool to improve the bioavailability of nutraceuticals. *Int J Mol Sci.* 2023;24(12):15764. doi:10.3390/ijms241215764.
- [148]. Wu X, Zang R, Qiu Y, et al. Intranasal drug delivery technology in the treatment of central nervous system diseases: challenges, advances, and future research directions. *Pharmaceutics.* 2025;17(6):775. doi:10.3390/pharmaceutics17060775.
- [149]. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. *Drug Deliv Transl Res.* 2022;12(4):735-57.
- [150]. League-Pascual JC, Lester-McCully CM, Shandilya S, Ronner L, Rodgers L, Cruz R, et al. Plasma and cerebrospinal fluid pharmacokinetics of select chemotherapeutic agents following intranasal delivery in a non- human primate model. *J Neurooncol.* 2017;132(3):401-7.
- [151]. Aderibigbe BA, Naki T. Chitosan-based nanocarriers for nose to brain delivery. *Appl Sci.* 2019;9(11):2219.
- [152]. Wong HL, Wu XY, Bendayan R. Nanotechnological advances for the delivery of CNS therapeutics. *Adv Drug Deliv Rev.* 2012;64(7):686-700.
- [153]. Uppuluri CT, Ravi PR, Dalvi AV. Design and evaluation of thermo-responsive nasal in situ gelling system dispersed with piribedil loaded lecithin-chitosan hybrid nanoparticles for improved brain availability. *Neuropharmacology.* 2021; 201:108832.