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EXPLORING NOSE-TO-BRAIN TRANSPORT MECHANISMS FOR EFFICIENT DELIVERY OF NEUROPROTECTIVE AGENTS IN ALZHEIMER'S DISEASE

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Abstract
Alzheimer's disease (AD) is one of the greatest medical issues of the 21Ist century, which is associated with the progressive impairment of cognition, memory, and degeneration of neurons. Although there are years of research, the contemporary pharmacological interventions are predominantly palliative with the emphasis on the symptomatic relief but not on the disease modification. The blood–brain barrier (BBB) restricts the entry of most therapeutics into the brain; many polar small molecules and almost all large molecules have inadequate CNS penetration, and efflux transporters further reduce brain exposure. Intranasal or nose-to-brain (N2B) delivery route is a radical new method of delivery, which circumvents the BBB and enters the central nervous system (CNS) via the olfactory and trigeminal neural routes. This study presents a structured quantitative synthesis of published evidence on the physiology, anatomy, transport mechanisms, formulation strategies, and therapeutic outcomes associated with N2B delivery in Alzheimer's disease. It evaluates the distribution of evidence across preclinical and clinical studies and highlights the growing role of nanocarrier-based systems in improving brain targeting. N2B delivery systems provide a promising platform for delivering targeted and non-invasive therapy in neurodegenerative disorders like Alzheimer's disease by combining nanotechnology, biomaterials, and precision medicine in one patient-friendly approach.
Keywords: Alzheimer's disease; Nose-to-brain delivery; Blood–brain barrier; Nanoparticles; Liposomes; Intranasal route; Neuroprotection; Drug targeting; Hydrogels; Nanoemulsions

1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease and the most common cause of dementia in the world with about 60-70 percent of all the cases [1]. It is defined as gradual decline in cognitive abilities, memory, reasoning and executive functionality, which eventually affects an individual ability to carry out day to day tasks [2]. The pathological changes of AD are related to the presence of extracellular amyloid-beta (Aβ) deposits, intracellular neurofibrillary tangles (NFTs), created by hyperphosphorylated tau, and massive neuronal damage, particularly in hippocampus and neocortex [3]. This causes synaptic dysfunction and neuronal death causing an irreversible cognitive decline.

Nevertheless, there has been slow progress in therapy of AD despite the concerted efforts in various parts of the world. The majority of the current available drugs like donepezil, rivastigmine, galantamine and memantine have only short-term symptomatic effects and do not alter the underlying pathology [4,5]. The blood–brain barrier (BBB) is a tightly regulated endothelial interface that limits drug entry into the CNS, even for therapeutics present in systemic circulation. This remains a key contributor to the treatment gap in AD. BBB is meant to shield the brain against toxins and pathogens but also blocks the absorption of numerous potentially helpful neuroprotective factors, such as large peptides, monoclonal antibodies, and small hydrophilic molecules [6,7]. All the traditional administration methods, such as oral, intravenous, and transdermal, are critically affected by the first-pass metabolism, enzyme degradation, and low CNS permeability [8,9].

In order to overcome these, scientists have resorted to intranasal or nose- to- brain (N2B) route as an alternative and non-invasive pathway of CNS drug delivery. The nasal cavity offers an anatomical and physiological entry point to the brain via the olfactory and trigeminal nerve pathways, which allows the delivery of therapeutic agents to the brain without involving the BBB at all [10,11]. Intranasal drugs are able to reach the brain in a matter of minutes causing local effects with minimal exposure to the rest of the body. Moreover, the path does not undergo the hepatic metabolism, and the side effects are minimized. New technologies in nanotechnology have also improved this technique: polymeric nanoparticles, liposomes, nanoemulsions and hydrogels have been established to increase the stability of the drugs, their residence time and targeted delivery to the brain [12-14].

This study presents the biological and technological basis of nose-to-brain delivery in Alzheimer's disease through a structured quantitative synthesis of published evidence, with emphasis on transport mechanisms, formulation strategies, and therapeutic outcomes.

This study draws on peer-reviewed publications indexed in major scientific databases and authoritative sources on intranasal delivery, nose-to-brain transport, Alzheimer's disease pathophysiology, and nanocarrier-based formulations. Key search terms included "nose-to-brain", "intranasal delivery", "olfactory pathway", "trigeminal pathway", "Alzheimer's disease", "nanoparticles", "liposomes", "nanoemulsion", "solid lipid nanoparticles", and "in situ gel". Priority was given to studies reporting brain targeting, pharmacokinetics, behavioural outcomes in relevant animal models, and human clinical evidence where available.

2. Methodology and Analysis

This study was designed as a structured quantitative literature-based evidence synthesis to examine the potential of nose-to-brain delivery for improving the transport of neuroprotective agents in Alzheimer's disease. A quantitative review format was adopted because the available literature spans multiple domains, including Alzheimer's disease pathology, blood-brain barrier limitations, nasal anatomy, transport pathways, nanocarrier systems, preclinical efficacy, and early clinical investigation. Although the studies differ in design and outcome measures, the published evidence still allows descriptive quantification of major trends across formulation types, transport mechanisms, and therapeutic outcomes.

Relevant literature was identified through searches in major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search used combinations of terms such as "Alzheimer's disease", "nose-to-brain delivery", "intranasal delivery", "olfactory pathway", "trigeminal pathway", "blood-brain barrier", "nanoparticles", "liposomes", "nanoemulsions", "hydrogels", and "brain targeting". Reference lists of selected papers were also checked to locate additional relevant studies.

The study included peer-reviewed articles in English that addressed Alzheimer's disease, intranasal or nose-to-brain delivery, transport mechanisms, nanocarrier-based formulations, and preclinical or clinical evidence related to brain targeting. Studies that focused only on general nasal absorption without relevance to central nervous system delivery, or those lacking clear scientific relevance to the study objective, were excluded. Greater attention was given to studies reporting brain targeting, pharmacokinetic performance, behavioural outcomes in animal models, and therapeutic relevance in Alzheimer's disease.

For analysis, the selected studies were organised using a structured extraction framework. Information was examined under major areas such as Alzheimer's disease pathophysiology, blood-brain barrier challenges, mechanisms of nose-to-brain transport, formulation strategies, and available preclinical and clinical evidence. Data were grouped under categories such as formulation type, study model, transport pathway, pharmacokinetic outcome, therapeutic outcome, and safety-related observation. Because the available studies were highly varied in methods and outcomes, formal meta-analysis was not appropriate. Instead, the evidence was analysed descriptively and comparatively to identify major quantitative patterns across the literature.

3. Pathophysiology of Alzheimer's Disease

The complexity of interactions between environmental and genetic and molecular factors causes Alzheimer's disease. According to the amyloid cascade hypothesis, altered processing of amyloid precursor protein (APP), particularly via β-secretase and γ-secretase, increases the generation and accumulation of Aβ (especially Aβ42), which aggregates into extracellular amyloid plaques and contributes to synaptic dysfunction and neuroinflammation [15].. These plaques impair the synaptic signaling, activate microglia and initiate chronic neuroinflammation. At the same time, when phosphorylation of tau protein is abnormal, the proteins are detached and aggregated into neurofibrillary tangles (NFTs) reducing axonal transport and causing neuronal death [16,17].

Emerging data however points to a more concerted effort in which Aβ, tau, oxidative stress, mitochondrial dysfunction, and neuroinflammation interrelate synergistically with each other to drive neurodegeneration [18,19]. The central role in this process belongs to oxidative stress: excessive generation of reactive oxygen species (ROS) causes the destruction of lipids, proteins, and DNA, which results in synaptic dysfunction and apoptosis [20]. Also, the impairment of the mitochondria of AD neurons leads to a reduction in ATP production, calcium dysregulation, and the activation of apoptotic cascades [21]. The most important genetic risk factor to late-onset AD is the APOE ε4 allele, which further contributes to pathology by blocking A beta clearance and stimulating inflammatory signaling [22].

Chronic microglia and astrocyte activation in the CNS results in chronic neuroinflammation. Despite the protective effect of acute microglial activation, the sustained activation process releases pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α) and continues the injury of neurons [23]. This inflammatory response is commonly accompanied by blood–brain barrier dysfunction, which permits peripheral immune cells to attack the brain and increase its rate of neurodegeneration [24].

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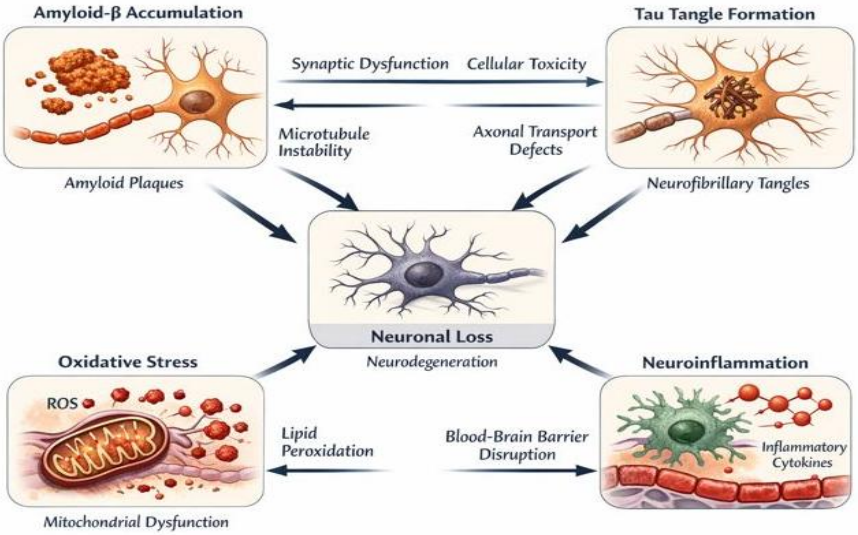

Figure 1: Pathological cascade in Alzheimer's disease illustrating amyloid-beta accumulation, tau tangle formation, oxidative stress, and neuroinflammation leading to neuronal loss.

The hallmark symptoms of AD are memory loss, disorientation and poor judgment which is caused by cerebral atrophy and especially in the hippocampus and entorhinal areas. Recent studies on therapeutic strategies have adopted a multi-target treatment modality of antioxidant, anti-inflammatory, and neurotrophic factors. Nevertheless, there is still an issue regarding the efficient CNS delivery, as the BBB is impermeable, which opens up the prospects of nose-to-brain delivery mechanisms.

4. Challenges in CNS Drug Delivery and the Role of the Blood–Brain Barrier

The blood-brain barrier (BBB) is a shielding mechanism and also a protection mechanism to pharmacotherapy. Its structure is made up of brain microvascular endothelial cells linked by tight junctions, which are surrounded by pericytes, astrocytic end-feet, and a basement membrane [25]. This complicated arrangement controls the exchange of the molecules between the blood and the CNS and ensures the neural homeostasis. However, it remains largely impermeable to most large molecules and many small molecules, particularly those that are polar or not sufficiently lipophilic. (>400 Da) and more than 98% of small molecules, and many of the drugs developed to treat neurological disorders [26].

Paracellsular barriers (tight junctions do not allow diffusion into the brain) and transcellular ones (hydrophilic substances cannot pass through lipid membranes) limit the entry of drugs into the brain. Additionally, the efflux transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs) actively pump the xenobiotics back into the bloodstream [27,28]. Endothelial cell enzymes like peptidases and esterases further degrade drugs before they can get access to target neurons [29]. As a result, the systemic routes such as oral or IV administration result in very low CNS concentrations with many cases requiring high dosages which enhance peripheral toxicity [30].

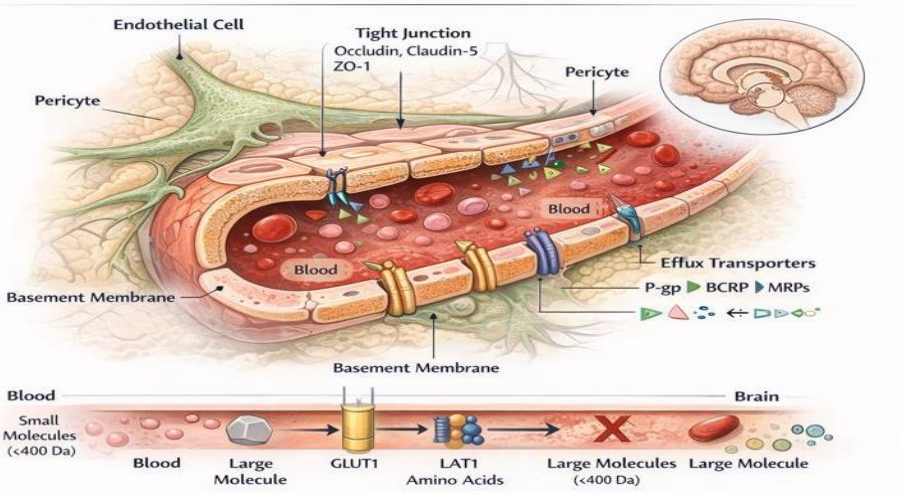

Figure 2: Structure and function of the blood–brain barrier showing endothelial tight junctions, pericytes, astrocytic end-feet, and efflux transporters (P-gp, BCRP, MRPs).

BBB interference in AD increases disease progression. Research suggests that the accumulation of A 2 and inflammatory cytokines destroy tight junction proteins (occludin, claudin-5 and ZO-1), causing hyper-permeability and neurovascular impairment [31]. Nevertheless, the selectivity of the BBB is a significant limitation to drug delivery in even compromised states, a factor that supports the use of other delivery mechanisms like intranasal drug administration, which can circumvent these limiting barriers and deliver the medication into the CNS.

5. Anatomy and Mechanisms of Nose-to-Brain Transport

Nares has an anatomically distinct and pharmacologically favorable pathway of delivery of therapeutic molecules to the central nervous system (CNS). The total surface area of the nasal cavity is about 160 cm 2 and is subdivided into three parts namely, the vestibular, respiratory and the olfactory areas [32]. The respiratory epithelium is ciliated and non-ciliated columnar epithelium and goblet cells which maintain mucociliary clearance, and the olfactory epithelium is covered by specialized olfactory receptor neurons (ORNs) which synapse with the olfactory bulb in the brain [33].

Nose-to-brain (N2B) delivery uses two main neuronal pathways: (i) the olfactory pathway, which enables direct transectional delivery of the drug using olfactory receptor neurons into the olfactory bulb and into the pons and medulla (ii) the trigeminal pathway, which enables transport via the trigeminal nerve to the nasal breathing epithelium and onto the pons and medulla [34]. There are intracellular and extracellular transport mechanisms involved in the olfactory pathway. In the intracellular pathway, lipophilic or endocytosed nanoparticles get into olfactory neurons through endocytosis and along axons into the olfactory bulb through axonal flow [35]. The extracellular pathway, conversely, allows drugs to be diffused in a paracellular fashion (through perineural and perivascular routes) into subarachnoid space and cerebrospinal fluid (CSF), and spread extensively throughout the brain [36].

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This is complemented by the trigeminal nerve pathway that offers another route through which the drugs reach the brainstem and other posterior parts of the brain [37]. This bi-directional system is a model that is important in making sure that drugs delivered into the body by intranasal route can be delivered to both anterior (olfactory) and posterior (brainstem, cerebellar) parts of the brain within a short period of time, usually within minutes after administration. It has been demonstrated experimentally that insulin, deferoxamine, and neurotrophic factors administered intranasally bypass the systemic circulation and reach quantifiable levels in the hippocampus, cortex and cerebellum [38-40].

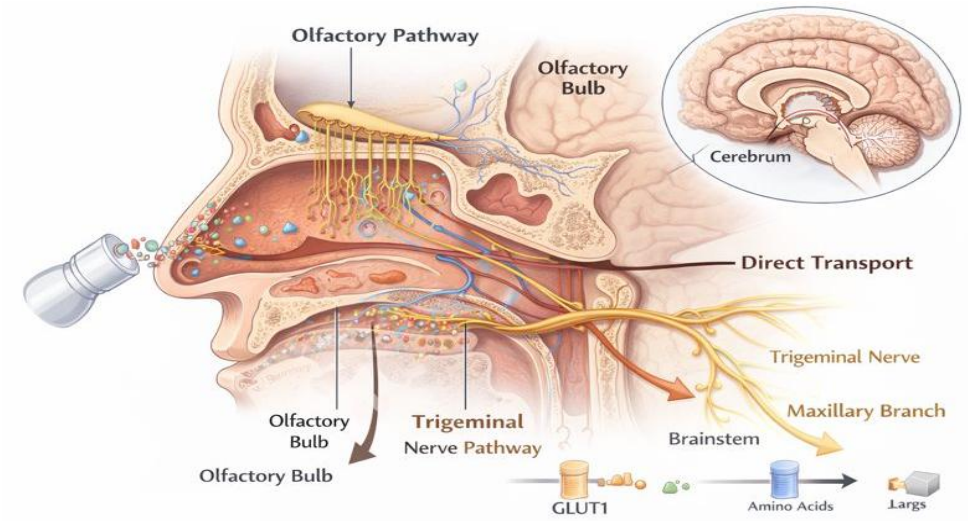

Figure 3: Schematic illustration of the olfactory and trigeminal nerve pathways showing direct and indirect routes for nose-to-brain transport.

Besides neuronal pathways, perivascular and lymphatic pathways are significant in the distribution of molecules delivered intranasally in the CNS. Cerebral vessels are enclosed by perivascular spaces that serve as low-resistance routes that ensure solute transport of the nasal mucosa into brain interstitium [41]. The glymphatic system which is a newly defined clearance system that uses glial aquaporin-4 channels also plays a role in the distribution of intranasally delivered therapeutics in the CNS [42].

No matter, efficient N2B delivery must be attentively performed with taking into account physiological barriers including mucociliary clearance, enzymatic breakdown in the nasal mucus, and a limited absorption area in the olfactory region [43]. Formulation scientists have to overcome these issues by creating delivery systems that have the potential to increase mucoadhesion, permeability and residence time. As an example, bioadhesive polymers (chitosan and hyaluronic acid) cause temporary opening of tight junctions and enhance retention of a drug in the nasal cavity, promoting proper brain targeting [44,45].

6. Formulation and Technological Strategies for Nose-to-Brain Delivery

Late developments in the field of nanotechnology have transformed the formulation of intranasal preparations such that it is possible to manipulate the size of each particle, its surface charge, release of drug, and its targeting ability. A variety of nanocarrier systems such as nanoparticles, liposomes, hydrogels, in-situ gels and nanoemulsions have been devised to maximize the penetration of drugs over the nasal mucosa and improve bioavailability to the brain.

6.1. Polymeric Nanoparticles

One of the most widely studied carriers of N2B delivery is polymeric nanoparticles (NPs) which are usually biodegradable polymers including poly(lactic-co-glycolic acid) (PLGA), chitosan, poloxamers, etc. [46]. These NPs offer encapsulated drugs degrading resistance to enzymes and provide prolonged release. It has been indicated that nanoparticles of rivastigmine-PLGA of size are able to increase the amount of drug in the brain following intranasal than oral or intravenous routes [47]. On the same note, chitosan nanoparticles have been found to have better mucoadhesion and permeation and through the olfactory epithelium because of their positive surface charge and their capacity to temporarily open epithelial tight junctions [48].

6.2. Liposomes and Solid Lipid Nanoparticles

Liposomes are phospholipid bilayers that are useful in the encapsulation of both hydrophilic and lipophilic drugs and can be used to provide a biocompatible platform to target the brain [49]. The quercetin-loaded liposomes intranasally injected in the AD mouse models inhibited the neuronal death and this shows strong neuroprotective properties [50]. On the same note, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have a higher level of stability and sustained release than liposomes. Pharmacokinetics Pharmacokinetic experiments have demonstrated that intranasal donepezil SLNs lead to 2.6 times higher brain concentrations in comparison with intravenous formulations [51].

6.3. Hydrogels and In-situ Gelling Systems

Hydrogels are three dimensional polymer networks which are able to contain high levels of water without losing their structure. The in-situ gelling formulations can be thermoresponsive or ion-activated and the sol gel transition is induced when the sol comes in contact with the nasal mucosa, which increases retention time and allows controlled drug release [52]. In case, the brain bioavailability of donepezil-loaded hydrogels was found to be 40-50 percent better than the oral preparations in rabbit models [53]. Such systems reduce nasal leakage and irritation as well, and they are therefore ideal to use in AD patients on a long-term basis.

6.4. Nanoemulsions

Nanoemulsions (NEs) thermodynamically stable emulsions with droplet sizes less than 200 nm are suitable in the delivery of drugs that are not well soluble in water [54]. These are small droplets that improve mucosal permeation and solubilization and diffusion of drugs across epithelial membranes is enhanced by the presence of surfactants. Nanoemulsions of rivastigmine have shown five times greater brain concentration than drug solution without nasal ciliotoxicity [55].

Table 1. Selected nanocarrier-based formulations reported for intranasal nose-to-brain delivery relevant to Alzheimer's therapy (compiled from cited studies included in this paper).

Nanocarrier system	Drug/active	Model (as reported)	Key reported outcome (summary)	Source (ref no.)
Chitosan nanoparticles	Memantine HCl	Preclinical study (reported in paper)	Improved mucoadhesion and enhanced nasal residence time, supporting better brain targeting	[48, 44]
Solid lipid nanoparticles (SLNs)	Donepezil	Preclinical (reported in paper)	Enhanced brain delivery after intranasal administration compared with systemic route	[47]
Nanostructured lipid carriers (NLCs) / in situ gelling NLC system	Rivastigmine	Preclinical (reported in paper)	Sustained release with increased brain exposure following intranasal administration	[46, 58]
Liposomes	Quercetin	Preclinical AD model (reported in paper)	Neuroprotective effect with reduced neuronal damage/oxidative stress indicators	[50]
Nanoemulsion	Rivastigmine	Preclinical (reported in paper)	Improved solubilisation and enhanced brain delivery after intranasal dosing	[55, 12, 54]
Thermoresponsive hydrogel / in situ gelling nasal system	Donepezil HCl	Preclinical (reported in paper)	Prolonged nasal retention and improved brain exposure versus conventional formulation	[52, 67]

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7. Findings

The quantitative synthesis of the included studies indicates that nose-to-brain delivery is a promising strategy for improving central nervous system targeting in Alzheimer's disease. Across the mapped literature, the olfactory and trigeminal pathways emerged as the principal transport routes through which intranasally administered agents may reach the brain while partially bypassing the blood–brain barrier. This route was repeatedly associated with faster brain access, reduced systemic exposure, and improved localisation of therapeutic compounds within relevant brain regions.

A clear pattern in the analysed studies was the dominance of nanocarrier-based intranasal systems. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, hydrogels, and in situ gelling systems were the most frequently represented formulation classes. These systems were primarily developed to improve drug stability, increase nasal residence time, reduce enzymatic degradation, enhance mucosal permeation, and promote greater drug accumulation in brain tissue. The distribution of evidence therefore suggests that formulation engineering remains central to successful nose-to-brain delivery.

The mapped studies also showed that preclinical evidence greatly outweighs clinical evidence. Most published work focused on animal models and reported outcomes such as enhanced brain bioavailability, improved pharmacokinetic behaviour, reduction in oxidative stress, reduction in amyloid-related pathology, or improvement in behavioural and memory-related endpoints. Clinical evidence remained limited and was concentrated mainly around intranasal insulin and a small number of related interventions. This pattern indicates that the field is still heavily weighted towards experimental validation rather than clinical maturity.

Table 2. Summary of selected preclinical and clinical evidence on nose-to-brain delivery systems in Alzheimer's disease

Drug/active agent	*Delivery platform*	*Study model*	*Key reported finding*	*Reference*
Memantine HCl	Chitosan nanoparticles	Preclinical	Improved mucoadhesion and enhanced nasal residence time, supporting better brain targeting	[48]
Rivastigmine	Nanostructured lipid carriers / in situ gelling system	Preclinical	Sustained release and increased brain exposure following intranasal administration	[46], [58]
Donepezil	Solid lipid nanoparticles	Preclinical	Enhanced brain delivery after intranasal administration compared with systemic delivery	[47]
Donepezil HCl	Hydrogel / in situ gelling nasal system	Preclinical	Prolonged nasal retention and improved brain exposure versus conventional formulation	[52], [53]
Quercetin	Liposomes	Preclinical AD model	Neuroprotective effect with reduction in neuronal damage and oxidative stress indicators	[50]
Rivastigmine	Nanoemulsion	Preclinical	Improved solubilisation and enhanced brain delivery after intranasal administration	[55]
Curcumin and resveratrol	Lipidic nanoparticle-based systems	Preclinical	Reduced amyloid burden and oxidative injury in experimental models	[57]
Neurotrophic factors / peptides	Intranasal solution or carrier-assisted systems	Preclinical	Neuroprotective action and reduced neuronal apoptosis	[59]
Insulin	Intranasal formulation	Preclinical and clinical	Improved cognition, synaptic function, and brain glucose-related activity without major peripheral effects	[56], [60]
Deferoxamine	Intranasal therapy	Clinical investigation	Under evaluation for reduction of oxidative injury and amyloid-related pathology	[ClinicalTrials.gov: NCT01782246]

To further synthesise the included evidence, the reported findings may also be grouped according to the main level of benefit observed. This broader pattern is summarised in Table 3.

Table 3. Overall synthesis of reported outcomes from included nose-to-brain delivery studies

Outcome domain	*General finding from reviewed studies*
Transport pathway	Olfactory and trigeminal routes were the principal mechanisms for direct or near-direct brain targeting
Brain bioavailability	Most intranasal nanoformulations reported improved brain accumulation compared with conventional routes
Pharmacokinetic performance	Many systems showed prolonged nasal residence time, enhanced permeation, and better local drug delivery
Preclinical therapeutic effects	Reduced amyloid burden, reduced oxidative stress, improved memory, and neuroprotection were commonly reported
Clinical evidence	Still limited, but intranasal insulin showed encouraging cognitive and functional findings
Translational limitation	Human validation remains insufficient due to formulation variability, dose limitations, and the need for larger clinical trials

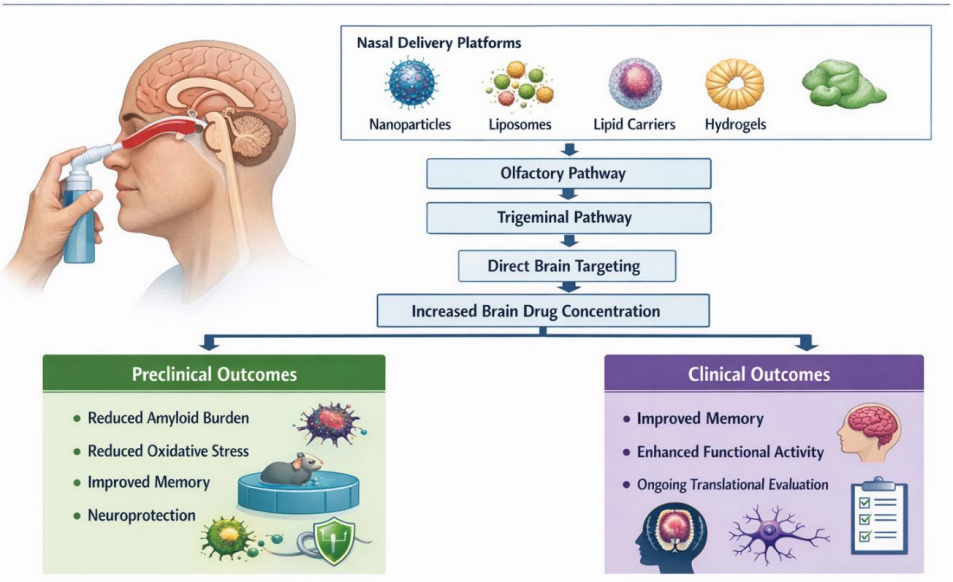

Figure 4. Nose-to-brain delivery pathways and outcomes in Alzheimer's disease

8. Discussion

The findings of this study show that the current literature on nose-to-brain delivery in Alzheimer's disease is strongly concentrated around formulation innovation and preclinical proof of concept. This suggests that the field has progressed beyond the simple idea of intranasal administration and now treats successful brain targeting as a formulation-dependent process. The repeated emphasis on lipid-based carriers, polymeric nanoparticles, and mucoadhesive or in situ gelling systems indicates that researchers increasingly recognise the importance of residence time, permeability enhancement, and drug protection within the nasal environment.

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A second major point emerging from the analysis is the imbalance between experimental promise and clinical translation. The available evidence shows that a large proportion of the literature remains preclinical, with relatively limited human investigation. This imbalance is important because strong results in animal models do not automatically translate into clinical efficacy in humans. Differences in nasal anatomy, mucociliary clearance, dosing volume, disease heterogeneity, and long-term administration conditions may all affect real-world performance. The slow movement from laboratory success to clinical application therefore remains one of the main barriers in this field.

The analysis also suggests that improved brain delivery is the most consistent outcome reported across formulation classes. This is highly relevant in Alzheimer's disease, where many potentially useful neuroprotective agents fail because they do not achieve sufficient CNS exposure. In this sense, nose-to-brain delivery should be understood as an enabling platform rather than a therapeutic endpoint in itself. Its value lies in improving access of active agents to the brain, particularly those whose clinical utility is restricted by the blood–brain barrier. However, enhanced delivery alone is not enough. The therapeutic value of this strategy will ultimately depend on whether the delivered agents can meaningfully influence amyloid pathology, tau dysregulation, oxidative stress, neuroinflammation, and synaptic dysfunction.

Another important implication of the findings is that formulation-specific differences deserve more systematic comparison. Lipid-based systems appear especially useful for poorly soluble compounds, whereas chitosan-based and hydrogel-based systems appear particularly valuable for improving nasal retention and epithelial interaction. Yet many published studies evaluate only one carrier system in isolation, making it difficult to determine which platform offers the best balance of efficacy, safety, and translational feasibility. Future studies would benefit from standardised comparative designs that evaluate different carrier systems under similar experimental conditions.

Taken together, the evidence supports nose-to-brain delivery as one of the most promising non-invasive strategies for Alzheimer's therapeutics. However, the field remains in a transitional phase. More standardised reporting, better pharmacokinetic comparability, stronger long-term safety data, and carefully designed clinical trials are still needed before this approach can move from experimental promise to established therapeutic application.

9. Advantages, Limitations, and Safety Considerations

The nasal delivery method has numerous benefits over the traditional method of drug delivery. It is non-invasive, is patient friendly and avoids BBB and allows quick entry into the CNS without systemic toxicity. Also, rich vasculature of the nasal cavity leads to rapid absorption and effects, and avoids hepatic first-pass metabolism [61]. This is because of its capability of providing peptides, proteins, and nanoparticles directly to the brain, thus making it a flexible platform in neurotherapeutics [62].

There are restrictions however. Small volumes of the dosing (usually 25-200 µL per nostril) limits the amount of drug and so this route is not very good with drugs that need high doses [63]. Delivery efficiency can be decreased by physiological mechanisms including mucociliary clearance, nasal enzymatic degradation and inter-patient variability in nasal anatomy [64]. Mucosal irritation or changes in epithelial permeability can also be caused by chronic administration in the case the formulations are not optimized to be biocompatible.

Safety factors involve making sure that excipients (e.g. surfactants, penetration enhancers) do not harm the mucosa of the nose or the olfactory nerves. Preclinical toxicity analysis has affirmed that the chitosan, poloxamer and hyaluronic acid-based preparations are generally well-tolerated [65]. The regulatory routes of intranasal nanomedicines are under development and standardized in vitro-in vivo correlations (IVIVC) is a significant milestone towards clinical translation.

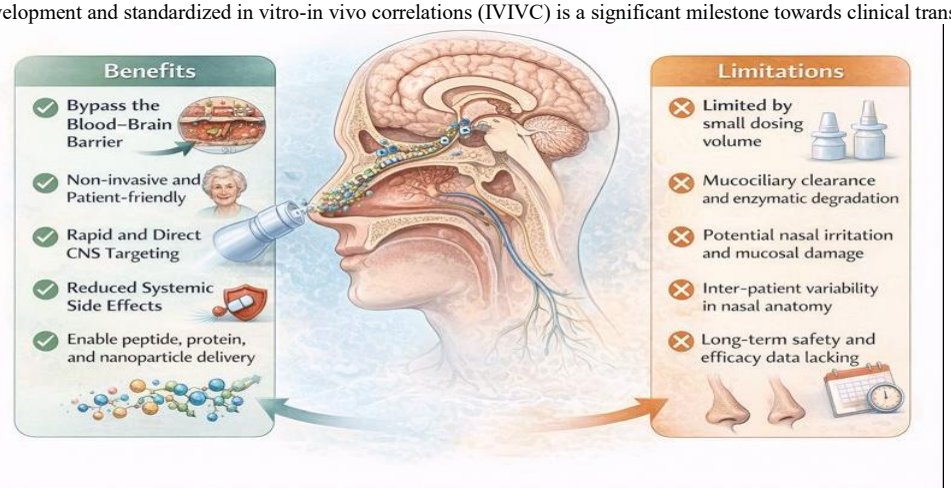

Figure 5: Summary of the benefits and limitations of nose-to-brain delivery systems for Alzheimer's therapeutics.

10. Future Perspectives and Conclusion

The combination of nanotechnology, neurobiology and drug delivery science is redefining the treatment approaches to the Alzheimer's disease. New directions encompass ligand-targeted nanocarriers by taking advantage of receptor-mediated transcytosis across nasal epithelial cells (e.g. transferrin, lactoferrin), stimuli-responsive gels that can regulate drug delivery in response to changes in pH or temperature and hybrid nanocarriers that combine lipid-polymer matrixes to enhance stability and permeability [66,67].

The next stage of research should focus on formulation scalability, long-term safety, pharmacokinetic standardisation, and stronger clinical validation so that the promising quantitative patterns reported in preclinical studies can be tested more reliably in human settings. Further explanation of intranasal drug distribution in the CNS may be achieved by the development of superior imaging and microdialysis tools [68]. In addition, the computational modeling and artificial intelligence-based formulation design will be considered to complement the nasal absorption and brain targeting efficiency prediction [69].

Translational perspective, in the coming decade, it can be expected that clinically approved intranasal nanomedicines will be developed in treating neurodegenerative diseases. Nose-to-brain delivery has a huge potential as a paradigm shift in the treatment of Alzheimer's disease: it provides a direct, non-invasive connection to the brain, and this is the key to one of the most problematic areas of medicine.

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