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Review

Nose-to-Brain Drug Delivery Strategies for Alzheimer's Disease: Advancing Therapeutic Efficacy and Patient Outcomes

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterised by memory disabilities, cognitive impairment, and dysfunction of neurons that can be attributed to the deposition of amyloid-β plaques and hyperphosphorylated tau protein buildup. Those pharmacotherapies available, namely donepezil, rivastigmine, galantamine, and memantine, are symptomatic and limited by a lack of optimal blood-brain barrier permeability. Constituting a non-invasive modality, nose-to-brain drug delivery represents an effective and promising alternative that avoids the BBB of drugs through the method of olfactory and trigeminal nerve routes to it, which allows the direct delivery of therapeutic agents into the central nervous system. The rationale of this method is as follows: the bioavailability of the brain is stimulated, preventing additional harm to the body, and increasing patient compliance. Scientific methods like nanoparticles, liposomes, micelles, hydrogels and mucoadhesive carriers also improve the stability of drugs, retention and controlled release further. The preclinical and early clinical trials have shown that intranasal delivery of molecules such as insulin, curcumin-loaded nanoparticles, and donepezil has the potential to enhance and improve cognition, reduce amyloid burden and provide neuroprotection. However, there still exist translational barriers, which include long-term safety, scalability, cost and approval to use chronically, intranasally. Individual differences that are genotype-dependent, especially in the case of APOEε4 carriers, point to the need for personalised treatment paradigms. The research in the future must focus on large-scale, stratified clinical randomised trials, systematic assessment of chronic safety, and adoption of digital tools for adherence. Altogether, nose-to-brain drug delivery is a revolutionary way of clinical AD therapy as it provides a patient-centered, efficient, and focused approach to enhance the therapeutic effect and improve the quality of life of sufferers.

Keywords

Alzheimer's disease, Neuroinflammation, Nose-to-brain delivery, Blood-brain barrier, Nanocarriers

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorderthat is characterised by cognitive impairment (cognitive decline), memory loss, and impaired brain function [1]. It can also influence other cognitive functions such asspeech ability, behavioural issues, and mental confusion [2]. It is caused by an abnormalbuildup of protein in the brain: amyloid plaques and tau tangles, which damage the neurons [3]. The clumps of protein that are located outside the nerve cells are called amyloid plaques [4]. These plaques are made upofbeta-amyloid, a smaller part of a larger protein that is the amyloid precursor protein (APP). In the normal condition, APP is disintegrated into small fragments, which are cleared. But in the case of AD, these fragments of beta-amyloid clump to form plaques. The tau tangles consist of a protein named tau within the cells that enables the stabilisation of microtubules,which are routes of transporting nutrients and other substances within the neurons. Tau in AD becomes hyperphosphorylated (phosphate group attachment). This makes tau lose its microtubulestabilisation capacity. This causes the tau protein to take a twisted form or form tangled structures within the neurons, also referred to as neurofibrillary tangles. This causes the passing of neurons and brain atrophy (shrinkage) [5]. One of the well-known causes of AD is genetics. Mutations in the APP, presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes cause Early-Onset Familial Alzheimer's (EOFAD) [6,7] whereas mutations in the apolipoprotein E (APOE) ε4 allele cause Late-Onset Alzheimer's (LOAD) and mutations in the APOE ε2 allele confer a reduced risk of this disease [8]. The cases that occur earlier, before age 65, are very rare,and they are known as early-onset AD. AD affect approximately 24 million individuals worldwide [9].

Current challenges in treatment: The only four drugs were estimated to be approved and used in treating AD- donepezil, galantamine, rivastigmineand memantine [10]. These drugs alleviate symptoms, without attacking two main characteristics of AD pathology: intracellular neuronal tangles (composed of rogue tau protein) and extracellular amyloid-β (Aβ) in plaques [11]. To enhance a patient's condition and quality of life, Alzheimer's patients need constant support and medicines [12]. For the treatment of moderate to severe AD, a memantine and donepezil combination medication has been approved. According to recent studies, combination therapy was the most successful in helping AD patients. However, it was also shown that the combination therapy increased the financial burden and was more costly than monotherapy [13]. One research literature involving 2,604 patients in nine trials revealed that the combination that involved cholinesterase inhibitors and memantine (NMDA receptor blocker) was more effective than that which involved cholinesterase inhibitors alone. Adverse event reporting however was limited, which should be improved in the future through improved monitoring [14]. The meta-analysis showed that the interventions of using both drugs together have shown significant improvement in saving the lives of the patients, and the typical adverse effects include nausea, vomiting and diarrhoea, which belong to the digestive system [15]. Lecanemab and Donanemab, two anti-amyloid antibodies, have been approved and put on the market as the first mechanistic treatments for AD [16]. In contrast to the previous antibodies that prevented the amyloid accumulation but failed to effectively remove it in the brain, the drugs are effective as they remove amyloid in the brain [17]. The therapy slows down but does not prevent the disease altogether. Amyloid-related imaging abnormality (ARIA), a significant side effect of medication that occurs in a small percentage of patients, is brought on by an inflammatory response when the antibody strikes the amyloid in the blood vessel walls. In any case, frequent MRI monitoring and visits to a specialist clinic are necessary for the ARIA, and these needs raise the cost of therapy [18,19]. Only those who are early in the disease process are now approved, and they need evidence of diagnostic accuracy about amyloid deposition as determined by either a PET scan or cerebral spinal fluid (CSF) biomarkers. Furthermore, it is still necessary to evaluate the drug's usefulness in different populations because the great majority of trial participants were white and of northern European ancestry [20].

Limitations of the conventional drug delivery methods: In central nervous system (CNS) disorders, medicines are usually given in a way that makes them enter the brain through the blood [21]. To achieve the desired concentration of the drug in the brain, patients have to increase the dosage or dose frequency. This may be toxic or lead to some side effects [22]. When the effect on the whole body is needed, the oral route is the most common and convenient method. But many drugs taken by mouth have problems, such as low absorption and first-pass metabolism (the liver breaking down the drug before it works properly) [23,24]. The primary challenges in treating dementia using conventional administration methods are the failure of molecules to pass through the blood-brain barrier (BBB) and the blood-CSF barrier. As a result, the brain is unable to achieve the desired therapeutic concentration. Tight connections between epithelial cells make up the BBB, which prevents any foreign substances from entering the brain [25]. Intranasal administration has been studied to deliver CNS drugs to overcome this physiological barrier.Some of the desirable characteristics of systemic effects are that it is not invasive, easily administrable, porous endothelial membrane, and has non-first-pass metabolism [26]. Most crucially, it can get straight to the brain without going through the BBB. The olfactory mucosa has direct contact with the brain and does not get protected by the BBB. Additionally, it may prevent systemic side effects by lowering the blood concentration and buildup of therapeutic medications in the primary organs [27].

2. Pathophysiology and Targets in AD

The pathophysiology of AD is characterised by two hallmark proteinopathies: Aβ plaques and neurofibrillary tangles formed by hyperphosphorylated tau. These pathological changes disrupt neuronal function and drive cognitive decline, as illustrated in Figure 1.

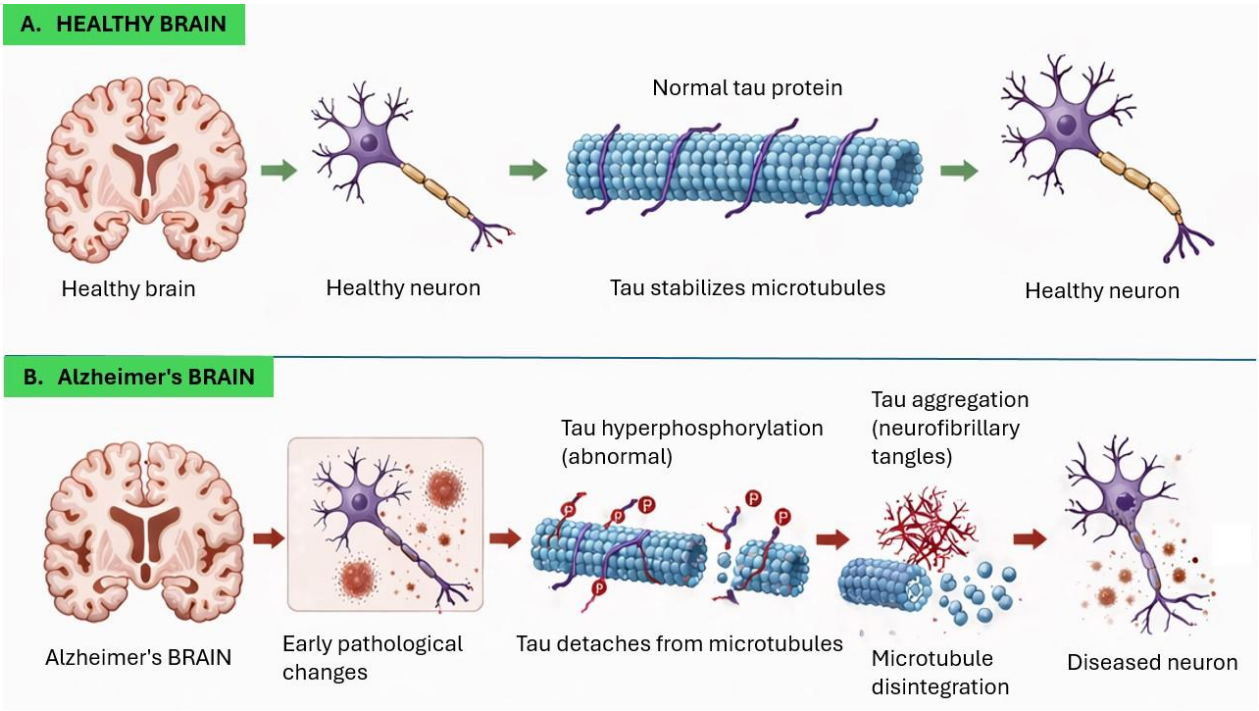

Figure 1. Pathophysiology of healthy brain versus Alzheimer's brain. (A) In the healthy brain, tau proteins are normally phosphorylated and bind to microtubules, stabilizing the cytoskeleton and supporting axonal transport, neuronal communication, and cell survival. (B) In AD tau tangles, and microtubule disintegration. These events impair axonal transport, cause synaptic dysfunction, and ultimately results in neuronal death and cognitive decline. Additional pathological features such as Aβ plaques and neuroinflammation contribute to disease progression.

2.1 Aβ Plaques and Tau Protein Hyperphosphorylation

The AD is a progressive disorder of the nervous systemthat majorly impacts memory and thinking. The pathogenesis of AD can be considered in terms of Aβ plaque formation as well as tau-induced development of neurofibrillary tangles [28]. In the healthy physiological state, neurons are signalled by dendrites, processed in the cell body, and then released by the axon to other neurons through the synapses [29]. The APP is a transmembraneglycoprotein that occurs in the neuronal membrane and is known to participate in the growth, survival, and repair of neurons [30]. The APP is proteolytically degraded with the help of α and γ secretase into soluble, non-toxic peptides, which breakdown easily [31].

The other type of processing occurs in AD. β-secretase (BACE1) catalyses APP cleavage followed by γ-secretase, releasing the Aβ peptides, Aβ42 which is highly hydrophobic and forms aggregates more readily [32]. The accumulation of these peptides results in insoluble Aβ plaques that are extracellular. These plaques disrupt the signalling of neurons and interfere with the synaptic transmission, and are coupled by the activation of the microglial cells [33]. These cells release pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), complement protein, and reactive oxygen species (ROS) that result in chronic neuroinflammation and BBB impairment that is linked to neuronal damage.

At the same time, intracellular tau protein, which stabilises microtubules under normal conditions, becomeshyperphosphorylated when Aβ accumulates to activate the kinase [34]. Hyperphosphorylated tau dissociates from microtubules, which leads to disassembly of the microtubules, axonal transport failure, and formation of paired helical filaments that accumulate into neurofibrillary tangles. The outcome of this, cytoskeleton is the breakdown and resulting dysfunction of the synapses and eventual neuron death [35].

2.2 Oxidative Stress

Oxidative stress is responsible for amplifying AD. It is caused by an imbalance between ROS and the accumulation of Aβ protein that disrupts the mitochondria's function [36]. It leads to decreased ATP production and overproduction of ROS. ROS are harmful moleculesthat cause lipid peroxidation, disrupt protein function, and damage DNA [37]. It promotes the death of neurons and increases the formation of amyloid plaque and tau protein tangles [38].

Early-onset familial AD is genetic. A mutation in the genes encoding PSEN1 and PSEN2, which are components of γ-secretase that increase the production of Aβ42. The mutation in the APP gene and the existence of the APOE ε4 allele increase the susceptibility to AD.

Together, such mechanisms of deposition of Aβ plaques, tau deposits, neuroinflammation, oxidative stress, and genetic susceptibility are the cause of extensive neuronal loss, cortical atrophy, and progressive impaired cognition that are hallmarks of AD [39].

2.3 Cholinergic and Glutamatergic System Dysfunction

Along with amyloid and tau pathologies, AD is associated with major changes to the neurotransmitter system. The degeneration of the basal forebrain cholinergic neurons causes a significant drop in acetylcholine, which disrupts memory, attention and learning mechanisms [40]. Simultaneously, the perturbation of glutamatergic transmission leads to hyperactivation of the NMDA receptor and release of calcium and excitotoxic death of neurons. These disturbances add to the synaptic dysfunction and cognitive loss [41]. It should be noted that they act as the pharmacological foundation of both present symptomatic therapy, including the action of cholinergic signalling enhancement in cholinesterase inhibitors (donepezil, rivastigamine, galantamine), along with the action of an NMDA receptor antagonist, memantine, that prevents excitotoxicity and restrains the progression of the disease of moderate to severe AD [42].

3. Mechanisms of Nose-to-Brain Drug Delivery in AD

The treatment of AD introduces great challenges because therapeutic agents are unable to go through the BBB in large amounts [43]. Non-invasive approaches adjacent to the BBB have taken a positive outlook in nose-to-brain drug delivery that allows direct delivery of drugs to the CNS [44]. The active exploitation of this method is possible based on the anatomical and physiological relationship between the nasal cavity and the brain that ensures a faster effect, fewer unnecessary exposures to the system, and more patient compliance [45]. There exist two key neuronal pathways: the olfactory and the trigeminal nerve pathways (Figure 2), which have a significant role to play in processing the transportation of drugs in the nasal cavity to the brain [46].

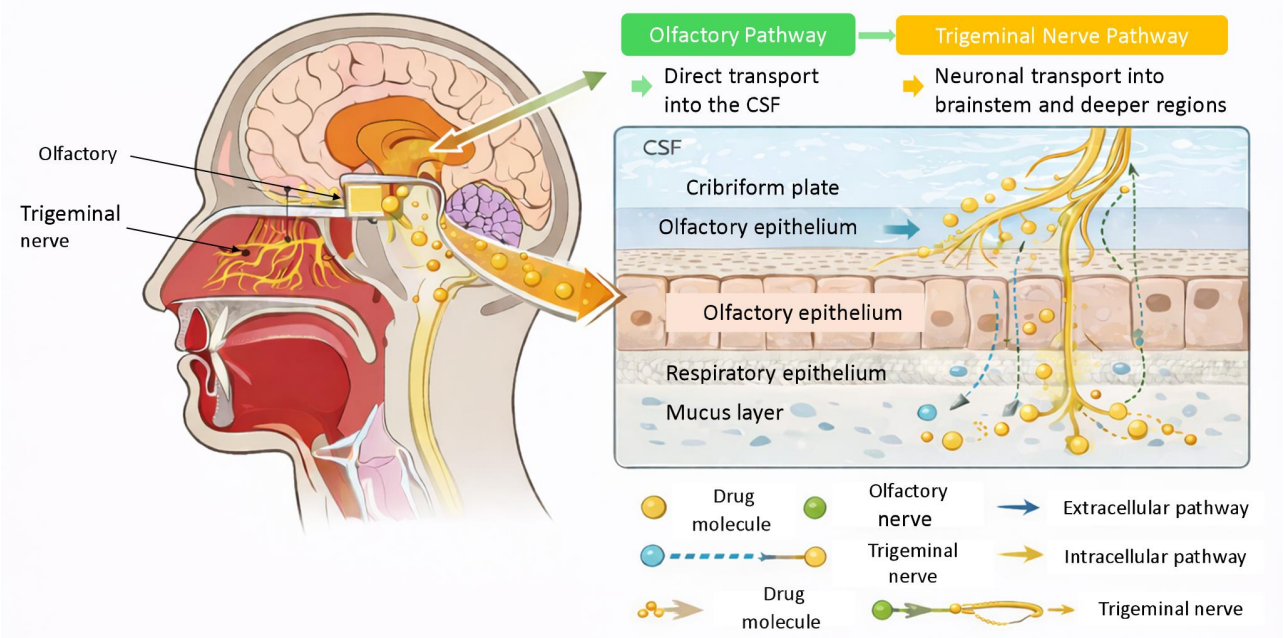

Figure 2. Direct pathway of nose-to-brain drug delivery. Intranasal administration allows drugs to bypass the BBB through two primary routes: The olfactory nerve pathway and the trigeminal nerve pathway. The figure also illustrates extracellular and intracellular transport mechanisms across nasal epithelium.

3.1 Olfactory and Trigeminal Nerve Pathways

3.1.1 Olfactory Nerve Pathway

The olfactory pathway is the shortest and the direct pathway towards the nose-to-brain drug delivery. The olfactory epithelium is found in the upper section of the nasal cavity, has axons crossing the cribriform plate of the ethmoid bone to reach the olfactory bulb [47]. The drugs that permeate across this specialised epithelium can enter by either paracellular translocation through the tight junction, which prefer smaller molecules, or by a transcellular mechanism: receptor-mediated endocytosis, for larger macromolecules [48]. Drugs can slow intra-neuronal axonal transfer into the olfactory bulb over hours to days once in the neurons, or they can use the even faster extra-neuronal perineural routes, through which CNS is delivered in a matter of minutes [49]. Once in the olfactory bulb, the drug molecules can diffuse to the brain parenchyma and cerebral spinal fluid, hence extensive dispersion to the CNS. Direct linkage makes the olfactory tract especially useful in delivering molecules thatcannot be otherwise transported by the BBB, such as peptides, proteins, as well as neurovitalizing agents used in the treatment of neurodegenerative illnesses [50].

3.1.2 Trigeminal Nerve Pathway

In addition to the olfactory pathway, the trigeminal nerve (cranial nerve V) is also vital due to the presence of the ophthalmic and maxillary branches in the nose-brain drug delivery by the invisible nerves due to the localisation to the respiratory and olfactory areas of the nose [51]. Drugs that get deposited here may be taken up by trigeminal nerve endings, followed by paracellular diffusion, transcellular uptake or axonal transportation to deeper CNS locations such as the brainstem, pons and spinal cord [50]. It involves both intra-neuronal and extra-neuronal routes, and diffusion across perineural trigeminal fibres offers a comparatively fast connection of the CNS. Agents affecting pain modulation, epilepsy, and neurodegenerative disease may be of particular importance in activating this pathway to supplement the olfactory pathway by extending the distribution profile to other parts of the brain that would otherwise be unable to enter [52]. The olfactory and trigeminal nerves collectively provide a dual and efficient bypass of the BBB and a wide-spreading exposure of the CNS following administration into the nose [53].

3.2 Direct Compared to Indirect Transport to the CNS

Direct or indirect transport Nose to the brain, can be transported either directly or indirectly. Direct transport deals with neuronal pathways (olfactory and trigeminal) going beyond the blood circulation and permitting drugs to get into the CNS in a few minutes [54]. It is a beneficial feature in such rapid delivery in the case of AD, where quick access to neuronal targets, such as a cholinergic system or aggregation of amyloid-B, might be essential in the treatment of alleviating to symptom control or disease modification [55].

In indirect transport, systemic absorption occurs via a highly vascularized mucosa of the nose, is then distributed by the systemic circulation and finally through the BBB trespassing occurrence. Although this is a slower pathway with a risk of being subject to first-pass metabolism, better bioavailability is still provided by this pathway as compared to administration through the mouth [56].

3.3 Applications in the AD

The nose-to-brain delivery of AD has great promise. Some of the cholinesterase inhibitors, neuroprotective peptides, insulin, and anti-amyloid agents have been investigated by means of intranasal administration [57]. The results of clinical research have indicated that delays in memory and increases in glucose metabolism of the brain were achieved after intranasal insulin was administered, lending credence to its therapeutic value. Furthermore, the method can minimise side effects of a peripheral nature, including nausea or cardiovascular problems that most oral or systemic drugs may cause [58].

All in all, nose-to-brain delivery has an excellent potential and is more palatable to patients and is an effective means of AD that provides the ability to efficiently target the brain with a minimal exposure to the systemic circulation. Additional improvement in the technology of formulations, such as nanoparticles, mucoadhesive gels, and in situ gelling systems, can also enhance the stability of the drugs, the retention time, and the transport efficiency, eventually leading to improved outcomes in AD.

4. Formulation Approaches for AD Therapy

4.1 Nanoparticles, Liposomes, Micelles and Hydrogels

The growing body of preclinical and early clinical studies has aimed at maximising cerebral delivery and therapeutic index of AD through targeted formulation technologies using hydrogels, liposomes, nanoparticles and micelles and mucoadhesive and permeation-enhancer approaches. In this section, recent literature reports on new formulation strategies to treat AD will be summarised.

4.1.1 Lipid and Polymeric Nanoparticles

The ability to safeguard therapeutic agents, offer controlled release, enable surface functionalization to support targeted delivery and deliver a wide range of cargos, including small molecules, siRNA or peptides, is what makes surface-engineered nanoparticles attractive [59]. Some of the polymeric systems that are widely studied include PLGA, PEG-PLGA and chitosan, as well as lipid-based formulations. The recent preclinical studies are examples of co-delivery of BACE1 siRNA with autophagy modulators or anti-inflammatory agents that can lead to better brain accumulation, less peripheral toxicity, and disease-modifying outcomes in AD models [60]. Nanoparticles are suggested to be used as multifunctional systems to co-deliver genes and drugs in vivo using peptides (e.g., transferrin or cell-penetrating peptides) or polysorbates to facilitate transcytosis across the BBB or nose-to-brain cell-penetration [61].

4.1.2 Liposomes

The abovementioned cargo versatility of liposomes, which is high (both lipophilic and hydrophilic compounds), as well as their biocompatibility and easy functionalization, still makes them attractive to AD therapy [62]. Comparative histograms of intranasal liposomal preparations of donepezil, memantine, and novel siRNA/protein cargos with

systemic preparations have shown enhanced cerebral biodistribution and behavioural efficacy in rodent models [63]. The BBB receptor-mediated transport can also be further improved by using ligand-targeted liposomes using transferrin or other similar receptor ligands, providing an effective delivery of systemically ineffective biologics, and permitting the repurposing of existing AD therapeutics with better CNS exposure [64].

4.1.3 Polymeric Micelles and Targeted Small Carriers

Self-assembled amphiphiles are polymeric micelles, which offer a small, consistent nanocarrier to hydrophobic CNS agents. New trends in research go beyond the passive presentation [65]. As an example, mouse models of ageing AD treated with borneol or terpene-modified micelles by taking advantage of transcellular routes and temporarily increasing the permeability of the BBB, have demonstrated less pathology and better cognitive performance [66]. Micelles can also able to be designed to release enzymes or acid-sensitive cargos based on local microenvironmental signals. Their properties render them highly appropriate in the provision of small hydrophobic modulators and phytochemicals that are under preclinical trials for AD [67].

4.1.4 The Hydrogel Systems and Depots

Hydrogels, also known as injectable, in-situ-gelling, or mucoadhesive matrices, serve as local depots of neuroprotective agents over an extended period, such as enzymes, antibodies or cells [68]. Intracerebral and intranasal hydrogel preparations of AD have been demonstrated to maintain the drug concentration in brain tissue or the tissue surrounding the olfactory/trigeminal pathways, hence lowering dose frequency and expanding therapeutic indexes [69]. Hydrogels that respond to stimuli, temperature, enzymes, or pH, can be used to release substances on demand or in response to the environment and have been used in animal models of neurodegeneration [70]. The hydrogel technique is especially beneficial when there is a need to have biologics exposed over a long period of time locally [71].

4.2 Mucoadhesive and Permeation Enhancer Technologies

Modern researchers are interested in mucoadhesive carriers such as chitosanand thiolated polymers to extend nasal residence time and enhance trans-olfactory absorption. The nasal (nose-to-brain) route circumvents the BBB and reduces the distance of the delivery route to olfactory and trigeminal nerves [72]. Pharmacodynamic and brain absorption have continued to be enhanced in AD models using chitosan-based powders and nanoparticles [73]. Current studies focus on reversible and least disruptive intensifiers to counteract long-term mucosal injury, which is a safety concern of paramount importance in long-term chronic AD therapy [74].

Collectively, these formulations explain the possibility of using a combination of nanocarrier systems and mucoadhesive systems to avoid the BBB and obtain long-lasting and directed therapy of AD (Table 1).

Table 1. Emerging formulation approaches for AD therapy.

Formulation Type	Key Features	Representative Materials	Mechanistic Advantages	Outcomes in AD Models	Refs.
Lipid and Polymeric (nanoparticles)	Nano-sized carriers with controlled release, and targeting	PLGA, PEG-PLGA, chitosan, lipid-based nanoparticles	Protect therapeutic agents, co-delivery agents, enhance BBB transcytosis	Enhanced brain accumulation, and reduce peripheral toxicity	[75]
Liposomes	Biocompatible vesicles for both hydrophilic and lipophilic drugs	Donepezil, memantine, and transferring targeted liposomes	Receptor-mediated BBB transport, and ligand-based targeting	Increased brain uptake, Improved behaviour, and enhanced CNS exposure	[76]
Polymeric Micelles and Targeted Small Carriers	Self-assembled nanosystems for hydrophobic drugs	Borneol or terpene modified micelles; enzyme or acid-sensitive micelles	Enhance BBB permeability, Controlled stimuli release	Reduced amyloid pathology, improved cognition	[77]
Hydrogels and Depot Systems	Injectable sustained release matrices	Thermo-/pH-sensitive hydrogels	Prolong local drug retention, adaptable release	Maintained brain drug levels, reduceddosing frequency, Extendedprotection	[78]
Mucoadhesive Systems	Nasal carriers enhancing mucosal uptake	Chitosan nanoparticles or powders, thiolated polymers	Bypass BBB via direct nasal route, boost absorption	Increased drug absorption and brain bioavailability, better efficacy	[79]

5. Recent Advances and Clinical Studies

Over the last few years, there has been a significant advancement in exploring novel treatment regimens and medication delivery systems to improve the patient's clinical outcomes in AD [80]. In their turn, the use of intranasal insulin,

curcumin nanoparticles, and novel formulations of donepezil are among the most promising ones, which are meant to enhance the pharmacological response by overcoming the limitations imposed by the BBB and classical systems of delivery [81].

5.1 Intranasal Insulin

The neuroprotective and neurotrophic effects of insulin intravenously have helped it to attract a lot of attention concerning its usage as a potential therapeutic tool in the treatment of AD [82]. Contrary to the systemic administration of insulin, through the method of intranasal administration, insulin is not transported across the BBB via the pathways via olfactory and trigeminal nerves; rather, the insulin must be directly delivered into the CNS. Based on this assumption, the following clinical research that was performed after the year 2021 has shown a promising display [83].

One can be found in a phase 2 randomised controlled trial, which explores old people using intranasal insulin in situations of mild cognitive impairment (MCI) and early AD [84]. In the study, the advancement of verbal memory and the maintenance of the hippocampal volume n were recorded in the participants administered an insulin dosage over a placebo group.Such estimations are consistent with previous studies, which indicated that insulin resistance in the brain causes cognitive deterioration and that insulin treatment can reverse this resistance [85,86].

However, the effectiveness of insulin in nose drops as a treatment method seems genotype-related. Those who had the APOEε4 allele responded to treatment less favorably than non-carriers, which highlights the value of individual medicine in future trials [87]. More recently, however, insulin detemir, which is a longer-acting analogue already under study, is designed to prolong the effect and increase patient adherence [88].

5.2 Curcumin Nanoparticles

The major bioactive ingredient of turmeric is curcumin, which is possessing anti-inflammatory, antioxidant, and anti-amyloidogenic properties in antiretroviral animal models of AD [89]. Although these benefits do exist, the need for this spice clinically has been hampered due to low solubility in water, poor absorption systemically and fast metabolism. The delivery systems based on nanotechnology have been designed to overcome these limitations [90].

Nanoparticles with curcumin and other solid lipid nanoparticles, liposomes and polymeric nanoparticles have exhibited increased BBB permeability, targeted cerebral delivery and systemic retention after a prolonged duration [91]. In a study conducted in 2023 and published in the International Journal of Nanomedicine, intranasal curcumin nanoparticles have been shown todownregulate the Aβ plaques and tau phosphorylation in transgenic AD mice with substantial improvements in the spatial memory levels [92].

The clinical research in humans is still in the initial stages, yet a pilot trial study shows that nano-curcumin is safe and potentially has cognitive effects. As an example, a randomised trial of older adults with MCI measured working memory and attention and found the positive effects of oral nano-curcumin supplement after 12 weeks [93].

Clinical trials on the future should produce the best dosage schedules, safety, and the most effective nanoparticle preparations to enhance therapeutic response. However, curcumin nanoparticles can be viewed as an inexpensive, risk-free, and readily available alternative for AD prevention and treatment [94].

5.3 Donepezil Formulations

Donepezil, a cholinesteraseinhibitor, remains an element of the ultimate symptomatic therapy of AD. Primarily, however, its usual oral route formulation is faced with low levels of penetration into the bloodstream and systemic adverse incidents like gastrointestinal side effects [95]. New methods of delivery, such as intranasal, transdermal and buccal, are being developed to improve cerebral targeting and minimise peripheral exposure [96].

In 2022, A journal article about the pharmacokinetics of an intranasal donepezil spray was published in the publication Alzheimer: Research and Therapy. The outcomes proved an accelerated rate of action, an increase in brain levels and a reduction of side effects in the system compared to the oral one [97]. Also, donepezil in the arrive of a transdermal patch, approved in Japan and South Korea, provides consistent plasma levels and adherence, especially in patients who have dysphagia [98]. Emerging studies are also in support of the creation of nano-end formulated donepezil, making use of polymeric nanoparticle or liposome to penetrate the BBB. These formulations, when delivered intranasally or intravenously, have shown increased neuroprotective ability in animals, such as the reduction of Aβ aggregation and increase of cholinergic signalling [99].

Another option is to include donepezil in the form of multiple drug nanoparticles in multi-drug systems, like adding memantine or antioxidants, and this is under investigation as its merits are pre-clinical [100].

Intranasal Insulin has emerged as an attractive treatment approach for AD owing to its neuroprotective and neurotrophic properties. Intranasal delivery of insulin allows direct delivery to the CNS via olfactory and trigeminal nerves, and this bypasses the BBB and reduces systemic side effects, in contrast to systemic (intravenous) administration.

5.4 Clinical Evidence and Trial Phases

5.4.1 Intranasal Insulin-Clinical Data

A phase II randomized controlled trial in Neurology assessed the effects of intranasal insulin in elderly with MCI and early AD. It showed enhanced verbal memory and maintenance of hippocampal volume in the treatment group versus placebo. The results are consistent with previous research that has implicated insulin resistance in the brain in the development of cognitive impairment and that insulin administration can be used to restore normal brain function.

Ongoing studies include those on insulin detemir, a long-acting insulin analogue in phase I/II clinical development to improve insulin duration of action and compliance [101,102].

Evidence: (1) Moderate to strong level of evidence from randomized trials (phase II); (2) Strong positive effects on cognition in a number of studies; (3) Backed by evidence of direct mechanisms of insulin signaling and neuroprotection; (4) Consistent results in pre-clinical and early clinical studie.

Limitations: (1) Few large-scale (phase III) clinical trials, limiting clinical confirmation; (2) Genetic variability: APOEε4 allele carriers have lower response; (3) Limited duration of trials, restricting knowledge on long-term CENP-E inhibitor.

Effectiveness and safety: (1) Different dosing and devices used in clinical trials; (2) Consistent procedures and larger and more diverse populations [103].

5.4.2 Curcumin Nanoparticles-Clinical Data

The major active component of turmeric, curcumin, has potent anti-inflammatory, anti-oxidant and anti-amyloidogenic effects in animal models of AD. But its use is hampered by its poor solubility, low oral bioavailability and rapid metabolism. To improve its brain delivery and effectiveness, nanotechnology-based formulations such as solid lipid nanoparticles, liposomes and polymeric nanoparticles have been developed [104,105].

Preclinical and clinical data (phases): One preclinical study (using animals) administered curcumin nanoparticles (intranasally) to transgenic AD mice. It found a decrease in the number of Aβ plaques and phosphorylation of tau, and improvements in spatial memory (endpoint: cognitive tests such as maze).

In humans, there are few studies. A phase I/II randomized clinical trial with older adults with MCI (n=30-60) examined the effects of 12 weeks' oral nano-curcumin supplementation. It showed positive effects on working memory and attention (primary endpoint: MMSE and other cognitive scales; attention tasks) as well as good tolerability.

Evidence: (1) Good preclinical evidence showing disease modifying effects (Aβ and tau reduction); (2) Preliminary phase I/II clinical evidence for safety and small effects on cognitive function; (3) Biologically plausible mechanism of action (antioxidant and anti-inflammatory); (3) Animal studies showing beneficial effects on biochemical and behavioural measures.

Limitations: (1) Absence of large (phase III) clinical trials validation; (2) Limited size of human trials, limiting statistical power; (3) Clinical trials of short duration (e.g., 12 weeks), too short to evaluate efficacy; (4) Human studies are mainly with oral delivery, but little clinical data with intranasal; (5) Different nanoparticle formulations lead to variability; (6) Very few studies on long-term safety, pharmacokinetics and dose.

5.4.3 Donepezil Formulations-Clinical Data

Donepezil, an Acetylcholinesterase inhibitor, is a commonly used agents to treat AD. But the oral route of administration leads to poor brain targeting, with known side effects including gastrointestinal problems. To address these challenges, other routes of administration, such as intranasal, transdermal and nanoformulations are being explored.

Preclinical and clinical data (phases): (1) Intranasal Donepezil (preclinical/early phase I). Intranasal delivery has shown to increase brain uptake and of rapid pharmacodynamic effects in preclinical studies in AD animal models (sample size: n≈20-40 per group). Readouts have been brain levels, decrease in Aβ and cognitive tests (e.g., maze). Phase I studies (small groups, n≈20-30) indicate better safety and lower systemic load than the oral form; (2) Transdermal Patch of Donepezil (phase II/III). A transdermal patch (available in Japan and South Korea) has been tested in phase II/III studies (n≈200-500). These have demonstrated steady plasma concentrations, improved compliance and fewer GI side effects. The majority of trials used cognitive tests (ADAS-Cog, MMSE) and safety/tolerability as primary outcome measures [106]; (3) Nanoformulated Donepezil (preclinical/early phase I). Donepezil loaded polymeric nanoparticles and liposomes have been tested in preclinical trials (n = 15-30 animals). These formulations exhibited increased brain penetration, decreased Aβ aggregation and increased cholinergic activation. Biochemical (Aβ levels), neuroprotection and cognitive behavioural assays were used as endpoints. Very limited phase I explorations are also underway in small groups of humans; (4) Combination Nanoformulations (preclinical). Combinational nanoparticle systems of donepezil and other compounds (memantine, antioxidants) are in the preclinical phase. These studies (n≈10-25 animals) show

synergistic effects on memory enhancement and neuroprotection, with the primary goal being to improve memory function and reduce oxidative stress.

Evidence: (1) Good evidence for transdermal (phase II/III clinical trials); (2) Some evidence for intranasal formulations (preclinical + early phase I); (3) Modest, but promising evidence for nanoformulations and combination therapies; (4) Generally improved efficiency and toxicity with systemic drug delivery.

Limitations: (1) Scant large phase III data for intranasal and nanoformulations; (2) Limited human data in early phase studies (small sample size); (3) Efficacy and safety assessed over short time-frames; (4) Inconsistency in design of formulations (nanoparticles, liposomes) impact on repeatability; (4) Regulation of new delivery systems complex; (5) Combinations lack clinical evidence and optimal dosing [106,107].

A summary of translational advances, clinical studies, and novel formulations in AD therapy is presented in Table 2.

Table 2. Translational advances, clinical studies, and novel formulations in AD therapy.

Theme/Intervention	Description	Key Findings	Translational Issues/Next Steps	Refs.
Mucoadhesive Nasal Platforms & Nanocarriers	Engineering of nasal and nanocarrier-based systems to enhance CNS delivery.	Improved therapeutic brain delivery and efficacy in preclinical AD models.	Scalability, safety (chronic intranasal use), dose targeting in aging mucosa, regulatory pathways.	[108]
Intranasal Insulin	Direct CNS delivery bypassing BBB via nasal route.	Improved memory, and hippocampal volume [APOE genotype dependent]	Genotype-specific and phase 3 trials;improved formulations.	[109]
Curcumin Nanoparticles	Nanoparticle carriers to boost solubility and brain penetration	Reduce amyloid plaques, tau phosphorylation, improved memory	Larger clinical trials, dose optimization, long-term safety, standardization.	[110]
Novel Donepezil Formulations	Alternative routes (intranasal, transdermal, buccal)	Faster action, higher CNS levels, fewer adverse effects	Clinical translation of new routes and combination NP system.	[111]

6. Challenges and Future Perspectives

Though the formidable progress is encouraging, some obstacles still exist preventing the mass implementation and ultimate effectiveness of new methods of treatment for AD. These issues are safety, scalability, and patient compliance, which are important elements in defining the next steps of AD therapy.

6.1 Safety Considerations

The issue of safety is also a major issue, particularly in ageing groups, which are usually victims of non-communicable diseases. Although nanosprays and intranasal treatments can be used to target the CNS more effectively, they also have side effects [112]. An example is intranasal administration, which can result in irritation of the mucosa, nasal congestion and even long- lasting loss of olfactory senses [113]. The concept of nanoparticles being biocompatible can lead to a build-up in the non-target organs or an unanticipated reaction of the immune system [114].

Moreover, there are also treatment interventions that involve anti-amyloid monoclonal antibodies (e.g., lecanemab and donanemab), linked to amyloid-related imaging abnormalities (ARIA) that may lead to cerebral oedema or microhemorrhages. Such side effects require frequent MRI follow-ups and increase the complexity and the treatment costs greatly [115].

Stable patient safety over the long term should rely on large populations of patients, extended with diversity of ethnicity, to confirm the extrapolability of such new treatments. Regulatory systems also have to be revised to suit any new, more modern drug delivery system, in which they must go through a thorough toxicology review [116].

6.2 Scalability and Cost

This is another major barrier to implementation due to scalability. A large amount of money is necessary to produce nanoparticle-based drugs, monoclonal antibodies, and this production process is highly demanding in the facilities, quality control, and high monetary obligations required. The challenges in production could restrict access because the prevalence of AD is rising in the low- and middle-income countries due to the extended life span [117].

Insulin or donepezil intranasal devices, though effective, should be easy to use, standardised, and affordable to be adopted in mass. Standardisation of dosing, shelf life and packaging will be important to standardise such solutions on a large scale [118]. The logistical challenges of early diagnosis and individualised treatment are conditions that need to be prepared by health systems. Most of the novel therapies are best left in early AD, where they would need PET scan confirmation or CSF biomarker confirmation that might not be accessible or expensive in the normal clinical use [119].

6.3 Patient Compliance

The other important variable that can combine with the treatment outcomes in AD is patient compliance. The cognitive impairment with AD can severely impact the memory or compliance of the patient with medication regimes, particularly those that involve taking several doses every day or wherein there are complicated methods for how to administer it [120]. One of the methods that could be evaluated as advantageous is the intranasal and transdermal delivery routes, as they are simple to administer. Transdermal patches, as an example, require less dosing than transdermal; caregivers find it easier to monitor them [121]. Nevertheless, they also have some drawbacks, one of them being an unwelcome feeling of skin irritation or detachment in hot climates.Patients or caregivers should have educational activities to enhance their response to newer treatments. It can be closed with the help of Smartphone-based reminders, the integration of wearable technologies and a caregiver support program. Furthermore, studies on weekly or once/longJeff patches in liquids would also improve the adherence in the future years [122,123].

6.4 Future Perspectives

6.4.1 Future Directions

Large-scale, genotype-stratified clinical studies should be a focus of future research to gain insights into individual responses in AD. A focus must also be given to long-term safety assessment of intranasal formulations to ascertain their safety profile for long-term use. Moreover, digital health technologies (e.g., remote monitoring devices and wearables) can improve patient compliance, facilitate dose adjustment and enable better clinical outcomes. And further combination strategies that combine nose-to-brain delivery with precision medicine will also enhance the prospects for disease-modifying interventions.

6.4.2 Translational Roadmap

Bringing nose-to-brain drug delivery from the bench to the clinic involves overcoming a number of challenges. These challenges include reproducibility in preclinical and clinical studies, efficient and economical manufacturing processes, and formulation stability. Adapting to changing regulatory requirements is also needed for new intranasal drug delivery systems like nanoparticles, liposomes, micelles, hydrogels, and mucoadhesive carriers. Consensus on dosing, delivery systems and clinical outcome measures will aid clinical development. Multidisciplinary partnerships between academia, industry and regulators will expedite drug development.

6.4.3 Clinical Applicability

Nasally administered drug delivery is a novel, non-invasive alternative to bypass the BBB and deliver drugs directly to the CNS through olfactory and trigeminal pathways. Intranasal delivery is safer and more tolerable than conventional treatments like cholinesterase inhibitors and memantine that offer symptomatic benefits only, and new drugs such as lecanemab and donanemab that are expensive and require frequent medical monitoring.

Intranasal insulin, curcumin nanoparticles and modified donepezil formulations are among recent clinical and preclinical studies showing improved cognitive function and potential disease-modifying properties. Next-generation delivery systems improve drug targeting in the brain, offer prolonged release and minimise peripheral side effects, thus improving efficacy and compliance.

7. Conclusion

One of the potential paths of systems that facilitate the development of a cure against AD is nose-to-brain drug delivery, which chiefly averts the constraints that the BBB sets on therapeutic agents. Traditional treatments, such as cholinesterase inhibitors and memantine, are only symptomatic in the treatment, but nowadays new participants like lecanemab and donanemab can address the amyloid pathology; they are still costly and require extensive observation.
Non-invasive delivery through the nose provides a route that allows direct access to the CNS through olfactory and trigeminal nerves, whereby drug administration limits side effects in the systemic body, determining drug efficacy. The advancements in formulations, such as nanoparticles, liposomes, micelles, hydrogel, and mucoadhesive systems, have proven to perform better targeting to the brain, deliver continuous release, and in patients, in preclinical and early clinical trials. However, there remain such challenges as translational, which include the long-term safety, scalability, cost-efficiency, and the necessity of regulatory adaptation. The recent developments in clinical studies related to intranasal insulin, curcumin-nanoparticle systems, and newdonepezil constructs indicate the promise of the technique in improving cognition and slowing down the process of the disease.

Research in the future must focus on large-scale, genotype-stratified trials, stringent long-term safety studies, as well as the incorporation of digital health monitoring in order to enhance adherence and curative results. Altogether, nose-to-brain solutions, used in combination with advanced formulation technologies and precision medicine models, have significant potential to change Alzheimer management by allowing safer and more efficient, as well as patient-centered treatment.

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Ethics Statement

This article is a review study and does not involve any human participants, animals, or identifiable personal data. Therefore, ethical approval and informed consent were not required.

Data Availability Statement

No new data were generated or analyzed in this study. Data sharing is not applicable to this article as no datasets were created or used during the current study.

Author Contributions

All authors contributed significantly to the conception, literature review, manuscript preparation, revision, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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