IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Drug delivery methods based on nanotechnology for the treatment of Alzheimer's disease

Sadia parvee, Vidhi Sharma, Mikhuli Chakravarty , Arindam Kolay

Nims Institute of Pharmacy, Jaipur, Rajasthan- 303121

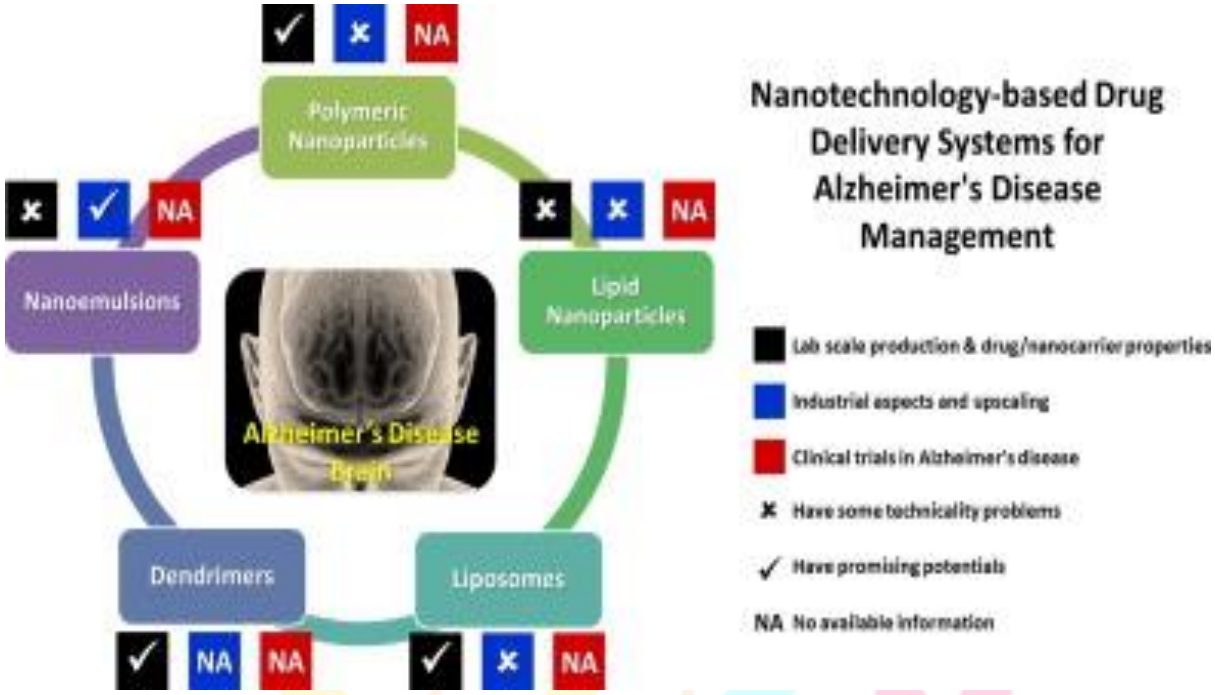
Abstract

Alzheimer's disease (AD) is a neurological condition that affects a large proportion of the older population in emerging countries, whose numbers are rising quickly. The majority of the FDA-approved pharmaceuticals now being sold for the management of AD symptomatology are traditional oral drugs. These medications and dose schedules limit patient compliance and cause therapy cessation because of their gastrointestinal side effects and ineffective brain targeting. It is common practise to ignore the industrial perspectives, processability, and cost/benefit analysis of employing NTDDS for AD treatment. Furthermore, considering that standard oral medication therapy is not producing satisfactory outcomes, active and passive immunisation against AD are by far the most researched alternative AD therapies. NTDDS of licenced medications seem to hold promise for moving this study from "paper to clinic" and giving hope to AD patients and their carers. This study's goal is to provide a thorough analysis of Alzheimer's disease drug delivery methods based on nanotechnology.

Keywords: Alzheimer's disease, nanotechnology; novel drug delivery.

Introduction

Alzheimer's disease (AD) is among the most significant medical and social issues affecting older people today, both in developed and developing countries. The neurotransmitter imbalance can be corrected using symptomatic medications for this illness. The symptoms of Alzheimer's disease and dementia are treated with a variety of medications, such as cholinesterase inhibitors, which reduce the breakdown of acetylcholine. Alzheimer's disease will likely be discovered in 6.5 million Americans 65 and older by 2022.The most prevalent kind of dementia affecting seniors is Alzheimer's disease (AD)[1,2].The diagnosis can be made in elderly people who have memory loss because it is a progressive neurological illness. Other symptoms may include cognitive dysfunction, communication difficulties, behavioural abnormalities, poor orientation, or coordination and feeding issues. Currently, AD is the sixth most common cause of mortality in the US and the fifth most common cause of death in Europe. It has a significant negative impact on the patients' and their families' ability to live normal lives and has significant financial ramifications. AD is now the sixth most common cause of death in the US, with 121,499 official death certificates issued in 2019. When AD affects a person younger than the age of, it is referred to as having a "early onset" (or "younger-onset"). A comparatively tiny proportion of patients have the early-onset form of Alzheimer's disease. The majority of them are in their 40s and 50s when the sickness first manifests. People generally live for eight years after their symptoms appear.[4,7].



The current course of treatment has a number of drawbacks, and intranasal medication delivery appears to offer a feasible alternative. The basis of currently approved medications for treating the cognitive deficits associated with AD is the regulation of neurotransmitters or enzymes. Acetylcholinesterase (AChE) inhibitors have gastrointestinal side effects such nausea and vomiting, which most frequently cause patients to stop taking their medication. Tacrine needs four doses daily because it has a short half-life. Additionally, due to hepatotoxicity, patients who used the medication needed routine blood monitoring. Furthermore, the half-lives of rivastigmine and galantamine are 7 and 2 hours, respectively.

Causes and Risk Factors of Alzheimer's Disease

Figure 1 shows a number of risk factors for AD, including advancing age, genetic predispositions, head trauma, vascular illnesses, infections, and environmental variables (heavy metals, trace metals, and others). Alzheimer's disease (A, NFTs, and synaptic loss) pathological alterations have an underlying cause that is currently unclear. Several theories were put up as potential causes of AD, however it is thought that two of them are the primary culprits[6].

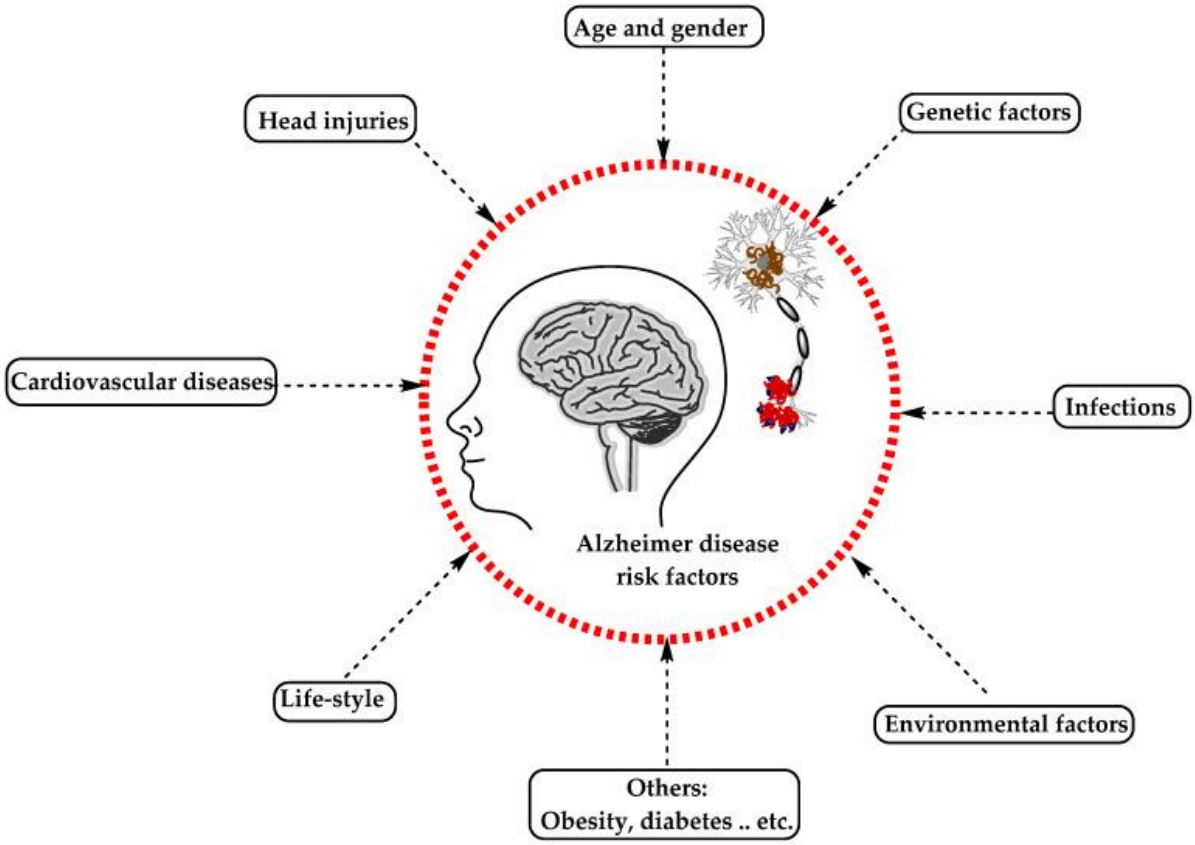


Fig: 1 The risk factors for Alzheimer's disease.

Neuropathogenesis, therapeutic targets, and treatments for Alzheimer's disease

The development of AD is gradual and delayed, and it may start 20 years or more before any clinical symptoms show up. The term "familial AD" refers to AD that may run in some families and makes up roughly 5–10% of all AD cases. The main genes for presenilins 1 and 2, alpha-2 macroglobulins, and Apo-E are those that are linked to familial AD. But sporadic (non-familial) AD, which makes up around 70% of cases, is brought on by a mix of genetic, environmental, and lifestyle factors[4,6].

Pathogenesis of AD

Identification of the targets for direct therapy and intervention in the earliest stages when the changes are reversible is crucial for a better understanding of the aetiology of AD. Intracellular neurofibrillary tangles and extracellular amyloid plaque development in the brain are the two most noticeable signs of AD onset. Hippocampal neuronal loss, synaptic degeneration, and aneuploidy are some of the histopathologic characteristics. As early pathophysiological changes in the development of AD, neuroinflammation, oxidative stress, microbial infection, mitochondrial dysfunction, and a damaged brain lymphatic system have also been identified (Swerdlow, 2007; Khoury and Grossberg, 2020). According to Harilal et al. (2019), a number of physiological factors, including those outlined in Figure 2, contribute to the development of AD. AD can advance more quickly due to lifestyle and aging-related variables. In order to comprehend the pathogenesis of AD, read the following subsections which detail these elements[5].

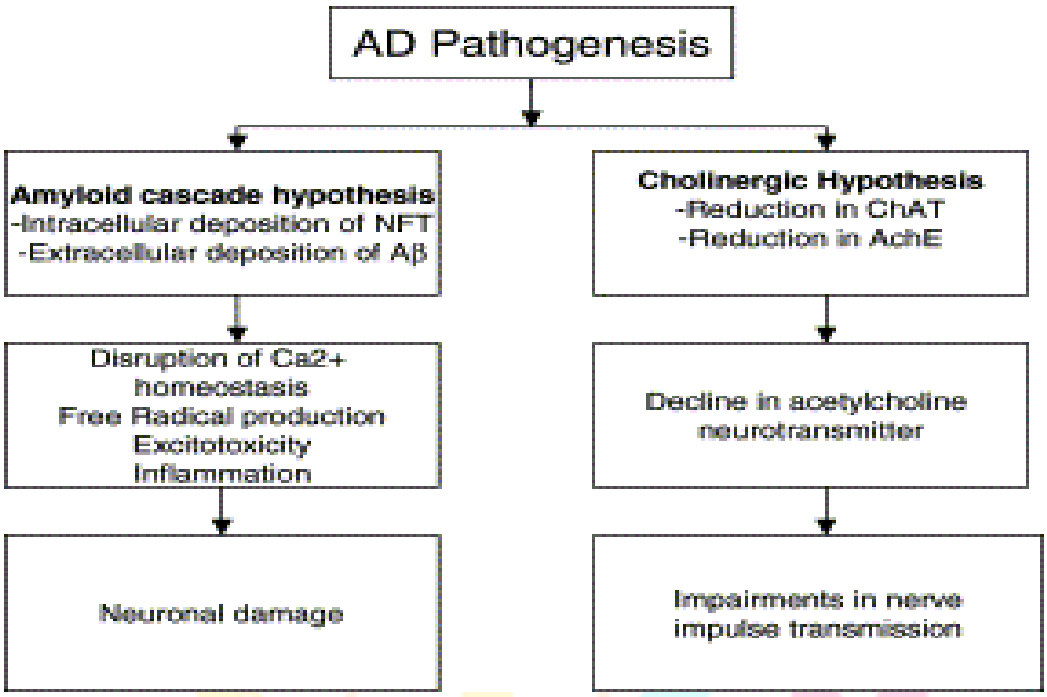


Fig2 : Pathogenesis of AD

Treatment of Alzheimer's Disease

Alzheimer's disease currently has no effective treatment. However, there are medications on the market that might momentarily lessen the symptoms[8].

Medicines

For Alzheimer's disease, a variety of medications may be used to help momentarily alleviate some symptoms.The main medications are.

- **Acetylcholinesterase (AChE) inhibitors**
  Acetylcholine, a chemical that aids in nerve cell communication, is produced in greater quantities in the brain as a result of these medications.
  For those with early- to mid-stage Alzheimer's disease, the medications donepezil, galantamine, and rivastigmine may be administered.According to the most recent recommendations, these medications should be continued until the later, more severe phases of the disease. Although there is no difference in the effectiveness of the three different AChE inhibitors, some patients may respond better to a particular type or experience fewer side effects, which can include nausea, vomiting, and appetite loss[10].
- **Memantine**
  There is no AChE inhibitor in this medication. It functions by obstructing the effects of too much glutamate, a neurotransmitter found in the brain. For Alzheimer's disease that is moderate to severe, memantine is prescribed. It is appropriate for people who cannot tolerate or cannot use AChE inhibitors.
  People with severe Alzheimer's disease who are already on an AChE inhibitor can also use it[8,9]. Constipation, vertigo, and headaches are possible side effects, however they are typically very short-lived. Read the patient information sheet that comes with your individual medication or chat with your doctor to learn more about any potential side effects[11].

Conventional regimens for the treatment of AD

Four cholinesterase inhibitors (ChE-Is) and one N-methyl-D-aspartate (NMDA) receptor antagonist have been approved by the FDA for the treatment of Alzheimer's disease. The last three ChEs are donepezil, rivastigmine, and galantamine; taurine is no longer available. When it comes to functional and overall

evaluation indicators, meta-analyses consistently outperform placebos. Drug-placebo differences in double-blind experiments persist for at least a year. Memantine and cholinesterase inhibitors have similar effects, enhancing cognitive performance above baseline and momentarily stabilising daily living tasks (ADL)[16]. The majority of research indicate that symptomatic medications reduce the onset of new neuropsychiatric symptoms while improving current neuropsychiatric symptoms. Numerous new avenues to improve cognitive function in Alzheimer's disease are being researched[20]

Challenges of Drug Delivery to the Central Nervous System

The physiological and structural features of the CNS currently obstruct prospective treatments for AD. Three physiological barriers in the CNS make it challenging for medications to cross them: I the blood-brain barrier (BBB), which is composed of capillary endothelial cells and joined by tight junctions; (ii) the blood-leptomeningeal barrier (BLMB), which contacts the cerebrospinal fluid (CSF) and has an unfenestrated endothelium connected by tight junctions; and (iii) the blood-cerebrospinal fluid (blood-CSF) barrier, which is made up Of Because of the BBB's poor permeability, chemicals can only pass through it if they engage with ATP binding cassette transporters and have certain physical and chemical properties. It is well known that BBB prevents 100% of large molecular weight medications and approximately 98% of low molecular weight pharmaceuticals from entering the brain. Due to the BBB's primary obstruction to drug delivery from the systemic circulation to the CNS, bioavailability in the brain is reduced, which results in ineffective treatment of neurodegenerative disorders[15,16].

New Therapeutic Agents

The difficulties of organising clinical trials to investigate the impact of medications on the progression of AD, as well as the requirement that clinical benefits be proved in terms of cognitive ability, make the discovery of novel treatment agents challenging. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1), glycogen synthase kinase type 3 (GSK-3), monoamine oxidase inhibitors (MAOs), phosphodiesterases, and the human monoclonal anti-amyloid antibody aducanumab are some of the new therapeutics that are currently being developed[

Current Strategies to Improve the Treatment of Alzheimer's Disease

Nasal Drug Administration

The prospect of non-invasive and simple drug administration has led to the nose route being recommended as an alternative to the parenteral and oral methods. Pathologies of the nasal cavity, including rhinitis, sinusitis, congestion, and allergic disorders, are treated with local medication administration. Since the nasal mucosa is generally porous and has ample blood perfusion, which allows for quick drug absorption into the bloodstream, systemic drug administration via the nasal route is also an option[19,20].

Figure 2 details the primary benefits and drawbacks of administering drugs via the nasal route

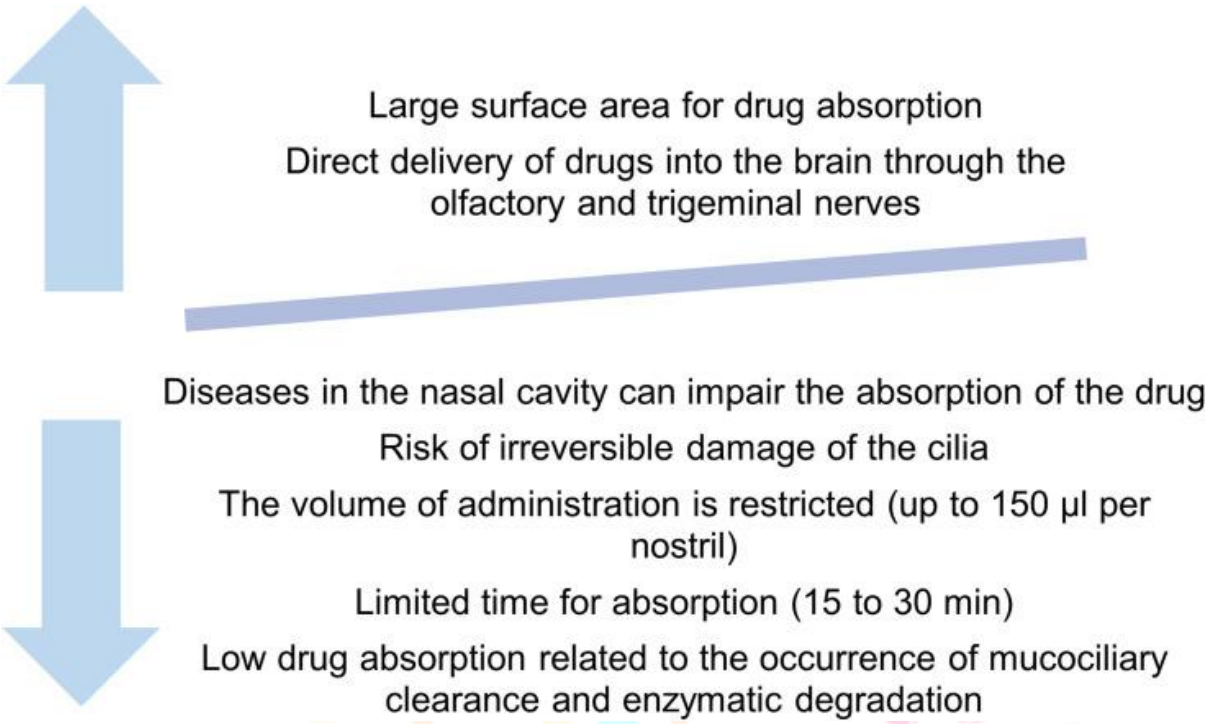


Figure-2 The main advantages and disadvantages of the nasal drug administration.

Conclusion:

The aforementioned therapies and drug delivery methods can reduce symptoms and severity, even if the condition cannot be totally cured. More developments and a deeper comprehension of these unique drug delivery methods and therapeutic approaches would be extremely beneficial to the globe, given the rise in AD-related fatalities and the exponential expansion in the number of patients. In contrast to parenteral and oral medication administration, the nasal route offers a viable method for managing AD. By administering medications nasally, the BBB is bypassed and the pharmaceuticals are delivered straight from the nasal cavity to the brain. Drug formulations need to have their physical-chemical properties tuned for this route of transport in order to have adequate brain bioavailability and to avoid the physiological nasal cavity clearance mechanisms. To increase drug absorption, several techniques have been researched. Drug transport from the nasal cavity to the brain has been accomplished using lipid-based nanosystems, such as nanoemulsions and NLC, with or without in situ-forming hydrogel matrices, according to recent research.

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