PEER REVIEWED

Intranasal Insulin for Alzheimer's:
Advancing Brain-Targeted Delivery

Alzheimer's disease (AD) represents a growing public health concern. While earlier estimates placed global prevalence of dementia at around 50 million people, more recent evidence suggests some form of AD may affect as many as 416 million people worldwide.[1] With increasing life expectancy and an ageing global population, this number is expected to rise even further in the coming decades, leading to increased demand on healthcare infrastructure and families.[1,2]

Growing Need for Multidisciplinary Treatment

Despite decades of research and global efforts to find a cure, treatment options for AD remain limited.[3,4] The amyloid cascade hypothesis – which implicates the accumulation of proteins in and around brain cells as the primary cause of AD – has long dominated therapeutic research.[5] This has led to the development of anti-amyloid antibodies, which have received regulatory approval in the United States for their ability to reduce plaque burden and slow disease progression.[6]

However, many trials have yielded mixed results, showing only limited impact on improving cognitive symptoms.[3,4,6] In addition, some individuals diagnosed with AD do not present significant plaque deposits, while others show pathological features without measurable cognitive impairment.[4] As a result, the clinical value of amyloid clearance is increasingly being questioned. A growing body of evidence now suggests that AD is a multifactorial syndrome rather than a single condition, involving a range of mechanisms including insulin resistance, hormonal changes, vascular dysfunction, and inflammation.[4,5]

In light of these limitations, there is an increasing interest in alternative therapeutic strategies that target different aspects of AD pathology. One such approach focuses on the role of insulin in the brain.[4,7]

Intranasal Insulin as a Promising Alternative

Research has shown that insulin signalling is disrupted in the brains of individuals with AD, a phenomenon sometimes controversially referred to as "type 3 diabetes"[4,7] Despite accounting for only 2% of the total body weight, the brain consumes approximately 20% of glucose-derived energy.[8] This high demand reflects glucose's central role in neuronal signaling.[4,8] Insulin signalling, in addition to facilitating glucose uptake into neurons, is also shown to directly affect neuronal upkeep, vascular regulation, synaptic signalling, and neuromodulation – all of which are relevant to cognitive functioning.[4,9]

Intranasal insulin (INI) presents a novel and promising method for addressing this dysfunction by delivering insulin directly to the brain via the nasal cavity.[7,9] This non-invasive, targeted approach has shown encouraging results in early clinical studies, with evidence suggesting it may improve memory and cognitive function, preserve brain volume, and improve AD biomarker profiles.[4,10,11]

Mechanism of Nose-to-Brain Transport

The effectiveness of INI depends largely on the unique anatomical and physiological features of the nasal cavity. Drugs delivered intranasally can access the brain through the olfactory and trigeminal nerve pathways. These routes allow for extracellular transport to the subarachnoid space and broader distribution throughout the central nervous system (CNS).[7,12]

This method of delivery is particularly valuable because it bypasses the blood-brain barrier (BBB), a highly selective barrier that prevents most drugs from entering the brain from the bloodstream.[13] Traditional approaches to bypass the BBB often involve invasive techniques or chemical modification of therapeutic agents, both of which pose additional risks and limitations.[13,14] In contrast, intranasal delivery offers a direct and non-invasive route to the brain.[7]

There are also significant safety benefits. INI avoids first-pass metabolism in the liver and minimises systemic exposure, reducing the risks of adverse events such as hypoglycaemia.[3,7] This localised approach helps to maintain insulin activity in people with AD where it is needed most, without significantly altering peripheral glucose levels.

Studies Demonstrate Feasibility and Safety of INI

To support the development of INI for human use, a preclinical study was conducted

using adult vervet monkeys to assess the biodistribution of insulin delivered via an intranasal device.[12] Researchers administered radiolabelled insulin using Aptar Pharma's Cartridge Pump System (CPS) and tracked its distribution using real-time PET imaging. This study demonstrated that INI via the CPS reached multiple key brain regions, including the amygdala, putamen, hypothalamus, and choroid plexus. Uptake in these regions was visible for up to 60 minutes post-administration, confirming successful and sustained delivery to the brain. No adverse safety signals were reported; vitals and blood glucose levels remained stable, and no signs of hypoglycaemia were observed. Additionally, whole-body radiation dosimetry showed low exposure across all organs, indicating a favourable safety profile.

These pre-clinical findings were supported by a similar PET imaging study in human participants.[15] This study included a mixed cohort of cognitively normal adults (n=7) and participants with mild cognitive impairment (MCI), both with (n=6) and without (n=3) evidence of amyloid-ß accumulation.

Results showed measurable brain uptake of radiolabelled insulin in regions associated with cognition and Alzheimer's pathology, including the hippocampus, amygdala, superior and middle temporal pole, and anterior cingulate cortex. Uptake varied based on cognitive status, sex, and vascular factors. As in the non-human primate study, no severe adverse safety signals were reported. Vital signs levels remained stable, with no signs of hypoglycaemia observed.

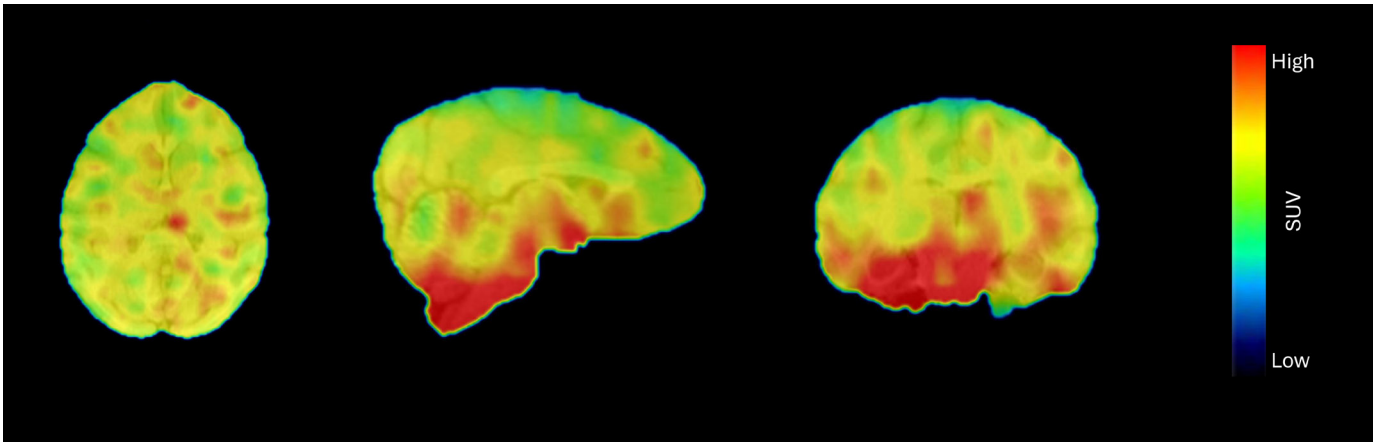
Optimising Delivery Systems for CNS-Targeted Intranasal Therapy

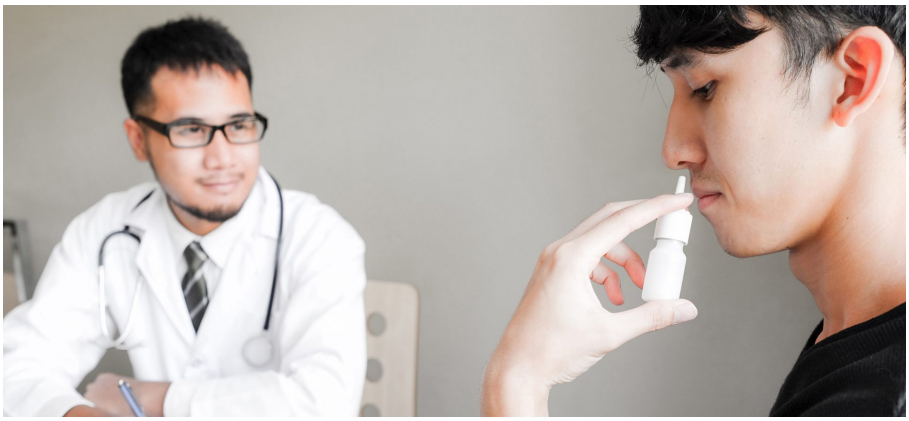
The promise of effective INI depends not only on the drug itself but also on how it is delivered.[7] Some nasal spray delivery devices, such as those used in allergic rhinitis, are not designed for CNS targeting. These systems tend to deposit medication in the nasal vestibule (the front part of the nasal cavity) rather than the upper nasal cavity near the olfactory region where absorption into the brain can occur.[16,17] As a result, much of the medication may be absorbed into systemic circulation, diminishing its effectiveness for CNS applications.[17]

To achieve consistent and targeted brain delivery, specialised intranasal systems are needed. These systems must be designed to navigate the complex anatomy of the nasal cavity and deliver medication with precision. This optimisation of nasal drug delivery for CNS applications is essential to fully realise the potential of INI in clinical settings.[16]

Although the CPS has demonstrated effective brain delivery via the olfactory and trigeminal nerves in non-human primate studies, unpublished *in vitro* nasal cavity model data suggest that its ability to deposit certain formulations in the upper nasal cavity may be limited. In the Wake Forest study, an add-on device was used to assist with positioning the spray within the nasal cavity, as the CPS itself was not specifically optimised for olfactory targeting due to targeted spray technology still being in its early stages.

Since then, advances in the field have led to the development and clinical validation of an olfactory-targeting nasal pump by Aptar Pharma. Nasal cast studies have shown optimised administration parameters such as spray geometry, plume angle, and particle size distribution which allow for improved deposition of the product to the olfactory region.[16,18] *In vitro* testing with a low-viscosity placebo formulation showed that Aptar Pharma's specialised nasal pump reaches up to 50% olfactory deposition under varied spray angles,[18] whereas the CPS achieves 4–27% in the olfactory at certain orientations as seen in unpublished data. Additional studies are needed to determine whether increased olfactory deposition could enhance insulin uptake and how it might affect the delivery of other formulations.





Future Directions for CNS Drug Delivery

As research progresses from preclinical to clinical phases, additional human studies will be essential to determine its therapeutic potential. These trials will need to assess safety, optimal dosing, and ultimately, clinical efficacy in slowing or improving cognitive decline. PET imaging and physiologically relevant modelling will also be instrumental in validating nose-to-brain delivery and guiding clinical development.

Beyond Alzheimer's the potential applications for intranasal brain delivery extend to other neurodegenerative and CNS disorders, including Parkinson's disease, epilepsy, migraine, and psychiatric conditions.[13] As a non-invasive, patient-friendly method, intranasal delivery for these therapeutic areas could enhance adherence and reduce overall treatment burden.[7]

Establishing a reliable and reproducible delivery method is not only critical for achieving consistent therapeutic effects, but also influences formulation strategies, patient experience, and regulatory pathways. The goal is to have a platform of products that meet different targeted zones to satisfy the requirements of different molecules and formulations. Tailored intranasal systems that ensure targeted CNS delivery may help derisk clinical programs and accelerate development timelines across multiple CNS indications.

Conclusion

Intranasal insulin offers a promising new direction for treating Alzheimer's disease and other CNS disorders. With growing evidence supporting its safety, feasibility, and brain-targeted efficacy, INI may fill critical gaps left by current therapies.

The ability to bypass the blood-brain barrier, deliver treatments non-invasively, and potentially improve cognitive outcomes positions INI as a compelling therapeutic strategy. As human trials progress and delivery technologies continue to advance, the pharmaceutical industry has a unique opportunity to lead the way in this evolving field of brain-targeted treatment.

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