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Small-Molecular Drugs for Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is predominantly characterized by the accumulation of β-amyloid (Aβ) plaques and the formation of neurofibrillary tangles, which are induced by the hyperphosphorylation of the Tau protein. Furthermore, the pathology of AD extends to include the progressive loss of synapses and neurons, accompanied by reactive gliosis. Mannose sodium capsule is a low molecular weight acidic oligosaccharide compound prepared from Marine brown algae extract. It is an innovative drug independently researched and developed by China with independent intellectual property rights, and has been supported by the national Major Special Project of New Drug Creation and Technology. Among the myriads of pharmacological interventions, Mannatna has emerged as a novel therapeutic agent the drug is the first novel drug targeting the brain-gut axis for the treatment of Alzheimer's disease in China and the world. Behind its development logic is a new understanding of the pathogenesis of Alzheimer's disease. that has notably demonstrated both its clinical safety and efficacy in Phase III randomized controlled trials. Post-marketing clinical studies have convincingly corroborated its effectiveness and safety profile across a diverse range of real-world patient populations.

Keywords: Alzheimer's Disease; Small-molecular; donepezil; rivastigmine; Sodium Oligomannate.

1. Introduction

Alzheimer's disease typically manifests sporadically and affects people beyond the age of 65. Age is the most reliable marker of the condition's progression. However, five to fifteen percent of cases are inherited, and fifty percent of cases start early and are strongly linked to certain genetic defects.The beginning and progression of the illness are linked to a minimum of five gene loci on chromosomes 1, 12, 14, 19, and 21. Mutations in the presenilin-I and presenilin-II genes, which encode the amyloid precursor protein, may be the cause of an autosomal dominant type of Alzheimer's disease, particularly early-onset dementia. Patients now experience abnormal processing of the amyloid precursor protein, which causes beta-amyloid fibril deposition and aggregation.Beta-amyloid protein makes up the majority of neurofibrillary plaques, which are made up of degenerated axons, oligodendrocytes, and dendrites around the amyloid core. Additionally, beta-amyloid protein can affect kinase and phosphatase activity by phosphorylating tau protein, a protein that stabilizes microtubules, and forming tau tangles. One of the extra gene determinants is the apoE epsilon (ε) allele.The Apo E protein affects nerve healing, the integrity of the cell cytoskeleton, and the buildup of beta-amyloid proteins. A person with two copies of the ε-4 gene has a much higher risk of developing Alzheimer's disease, but individuals carrying the ε-2 allele have the reverse impact.

An increased risk of Alzheimer's disease has been linked with smoking, diabetes, hypertension, and dyslipidemia. A increasing amount of research indicates that proactively treating these risk factors in middle age can lower the likelihood of cognitive impairment in the future.

Two pathogenic characteristics of Alzheimer's disease are:
(1) The extracellular deposition of beta-amyloid protein.
(2) Intracellular neurofibrillary tangles.

The deposition of beta-amyloid protein and the creation of neurofibrillary tangles cause synaptic and neuronal loss, leading in significant atrophy in the afflicted parts of the brain, which usually begins in the temporal lobe. Beta-amyloid peptides and neurofibrillary tangles are thought to induce this damage, although the exact process is unknown. Several hypotheses have been offered.

(1) According to the amyloid hypothesis, the cumulative buildup of beta-amyloid causes a complex cascade of events, including neuronal cell death, synapse loss, and increasing neurotransmitter deficit, which eventually leads to clinical dementia symptoms.
(2) The cerebral cortex of Alzheimer's patients exhibit inflammation and a chronic immune response. According to several experts, inflammation constitutes a third major pathogenic aspect of Alzheimer's disease.

(3) It has been demonstrated that abnormalities in the metabolism of sugar may be crucial in the onset of Alzheimer’s. Alzheimer’s disease has also been connected to the prion process. Proteins that are misfolded in prions can cause other proteins to misfold as well, increasing the amount of aberrant proteins and causing brain damage in the course of events. Both tau protein deposits within neurofibrillary tangles and beta-amyloid protein deposits within amyloid plaques in Alzheimer's disease have properties akin to self-replicating prions [1].

For certain people, cholinesterase inhibitors can partially improve cognitive and memory deficits. Four medications are in stock. Tacrine is infrequently used because of its hepatotoxicity, but donepezil, rivastigmine, and sodium oligomannate are generally as effective.

2. Donepezil

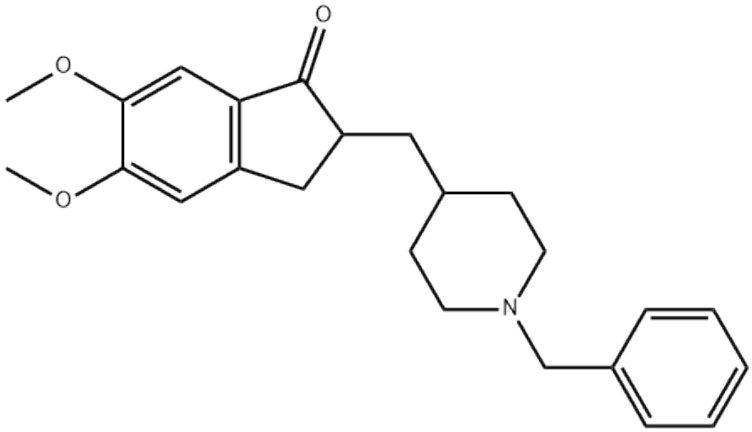

Figure 1. The structure of donepezil [2]

Donepezil is a member of the class of drugs known as cholinesterase inhibitors, which improves the effects of the neurotransmitter acetylcholine by inhibiting the enzyme that breaks it down (**Figure 1**.) [3].

2.1. Mechanism of Action

Donepezil improves the effects of the neurotransmitter acetylcholine by blocking the enzyme that breaks it down. Acetylcholine deficiencies are thought to impair daily function and contribute to the development of Alzheimer's disease. Donepezil is known as a powerful and fast reversible selective noncompetitive inhibitor of acetylcholinesterase (AChE). Although the clinical implications of AChE's selectivity in comparison to butyrylcholinesterase (BuChE) are unclear, it is widely believed that BuChE may compensate for AChE's function in the brain, notably in Alzheimer's disease (AD).Selective inhibitors of AChE have been shown to increase cortical AChE levels while decreasing Aβ peptide concentrations in the brain.Donepezil, a quickly reversible inhibitor, binds to AChE's hydrophobic binding sites, leaving the enzyme intact. In this reversible dynamic, neither the inhibitors nor the enzyme change state. As a result, for quickly reversible inhibitors, there is an inverse connection between drug concentration and enzyme inhibition, which is commonly shown visually as mirror images. The presence of the medication inhibits enzymes, therefore the pace at which the drug is removed is critical to understanding its pharmacokinetics [4].

2.2. Pharmacokinetics

Following a single injection, the pharmacokinetic profile of donepezil demonstrates a dose-proportional and linear distribution. The average terminal half-life of donepezil is 81.5 ± 22.0 hours, while its mean peak plasma concentration (Cmax) is 4.1 ± 1.5 hours. The post-absorption phase plasma concentration-time curves for the 4.0 mg and 6.0 mg administrations exhibited a biphasic pattern; however, the donepezil clearance rate was consistent at each dose. A full characterization of these lower dosages was not possible because plasma concentrations in the 0.3 mg, 0.6 mg, and 0.9 mg dosage groups were often below the high-performance liquid chromatography (HPLC) detection threshold, which was established at 2.0 ng/ml.The degree of inhibition of acetylcholinesterase (AChE) was significantly correlated with donepezil plasma levels. Between 33% and 35% of the donepezil groups' maximal AChE inhibition (Emax) were seen in the 4.0 mg and 6.0 mg ones. The levels of donepezil in plasma had a significant association with AChE inhibition [5].

2.3. Animal studies

With an emphasis on learning and memory, the study sought to determine the ideal donepezil dosage to inhibit acetylcholinesterase and improve mouse cognitive function.Peak plasma concentrations of 1.2 ± 0.4 hours and 1.4 ± 0.5 hours, respectively, with an absolute bioavailability of 3.6% were achieved by oral administration of donepezil at dosages of 3 and 10 mg/kg. In hairless rats, donepezil treatment decreased AChE activity by 31.5 ± 5.7%.Notably, donepezil concentration was found to be inversely related to plasma AChE activity.Its impact on cognitive abilities was assessed in mice using Y-maze equipment.Dosing mice with 3 mg/kg donepezil significantly delayed scopolamine-induced memory loss.Then found icreases in brain donepezil levels corresponded with a marked recovery in spontaneous alternation rate.The maximum effective donepezil dose in brain tissue was 46.5 ± 3.5 ng/g, allowing accurate prediction of its AChE inhibition and pharmacological effects. A concentration of 46.5 ± 3.5 ng/g has potential in improving learning and memory in animal models[6].

2.4. Clinical trial results

In phase I and II studies, donepezil showed a good pharmacokinetic, pharmacodynamic, and safety profile; older patients and those with renal or hepatic impairment did not need dosage changes.A straightforward once-daily dosage schedule is also made possible by the drug's lengthy half-life. Two pivotal, randomized, double-blind phase III trials that demonstrated significant improvements in global and cognitive functioning in patients with mild to moderate Alzheimer's disease treated with either 5 or 10 mg/day of donepezil compared to placebo were conducted after promising phase II clinical trial results.In phase II and III investigations, the majority of adverse effects were moderate, transitory, and cholinergic; they resolved with continuous administration of donepezil.Based on clinical research, donepezil is a well-tolerated, once-daily medication that effectively treats mild to moderately severe Alzheimer's symptoms [7] .

2.5. Side effects

Adverse effects seen clinical trials account for 20%-60% of patient, but the prevalence of such events in the treated population ranges from 10% to 70%, depending on the nature and degree of adverse drug reactions. Donepezil side effects and ADRs are divided into two categories: common side effects, which were discovered primarily in clinical trials involving Alzheimer's disease patients, and infrequent or exceptional side effects, which may occur under specific conditions or among small subsets of patients with varying medical conditions who are also taking adjunctive medications.More than 5% of patients receiving donepezil experience adverse drug reactions (ADRs) most commonly: physiological event, cardiovascular problems, gastrointestinal disorders, hematological and lymphatic abnormalities, metabolic and nutritional changes, musculoskeletal problems, respiratory problems, dermatological problems affecting the skin and appendages, special sensory deficits, urogenital problems [8] .

3. Rivastigmine

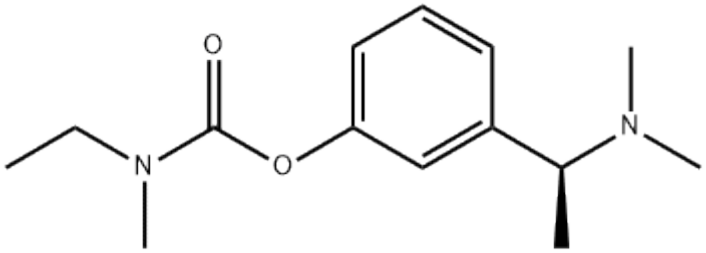

Figure 2. The structure of Rivastigmine[9]

Rivastigmine's target is acetylcholine (Figure 2.). Acetylcholinesterase quickly hydrolyzes the acetylcholine neurotransmitter delivered into the synaptic cleft, terminating signal transduction at the neuromuscular junction. Involvement in neuronal apoptosis.

3.1. Clinical trial results

In individuals with severe Alzheimer's disease (AD), the 24-week ACTION study evaluated the safety, tolerability, and efficacy of a 13.3 mg/24 h rivastigmine patch vs a 4.6 mg/24 h patch by randomization and double blinding. 716 out of the 1014 people that were tested were randomized to either the 4.6 mg/24 h patch (N = 360) or the 13.3 mg/24 h patch (N = 356). For both groups, the baseline characteristics and demographic information were equal.For the 13.3 mg/24 h group, 64.3% (N = 229) and 65.0% (N = 234) were the respective percentages.At Weeks 16 and 24, which acted as the primary endpoint ($P < 0.0001$ for cognition and $P = 0.049$ for function), the 13.3 mg/24 h patch performed better in cognitive function and daily functioning than the 4.6 mg/24 h patch ($P = 0.025$ for function). $P = 0.0023$ on the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change revealed significant differences between the two groups at week 24, whereas $P = 0.1437$) on the Neuropsychiatric Inventory - 12 (NPI-12) did not show any changes.Finally, improvements in cognitive and functional outcomes were achieved more successfully with the 13.3 mg/24 h rivastigmine patch than with the 4.6 mg/24 h patch, and adverse effects were not significantly increased.These data imply that the higher-dose rivastigmine patch has a good benefit-to-risk ratio for individuals with severe Alzheimer's disease [10] .

3.2. Adverse effects

Similar to other inhibitors of cholinesterase, rivastigmine was associated with cholinergic side effects most of the time. In clinical studies, rivastigmine was administered at dosages ranging from 6 to 12 mg per day. Approximately 14% to 50% of patients had these adverse effects, which included symptoms including nausea, vomiting, diarrhea, and anorexia, compared to 2% to 11% in the placebo group.Other adverse effects that were statistically significantly more common in rivastigmine users at the previously indicated doses as compared to the placebo group were headache, fatigue, somnolence, sweating, dyspepsia, sinusitis, and dizziness.The majority of these occurrences were classified as mild to moderate in severity, dose-dependent, and of short duration.Approximately 25% of individuals receiving rivastigmine at dosages ranging from 6 to 12 mg per day stopped treatment owing to side effects. Notably, one incidence of severe vomiting resulting in esophageal rupture was recorded after an improper resume of rivastigmine at a dosage of 4.5 mg following a several-week treatment gap.Despite these side effects, no clinically significant changes in laboratory measures or vital signs, including liver enzymes, were seen at the 6 to 12 mg per day dosage of rivastigmine; nonetheless, about 20% of patients had a 7% weight loss [11] .

4. Sodium Oligomannate

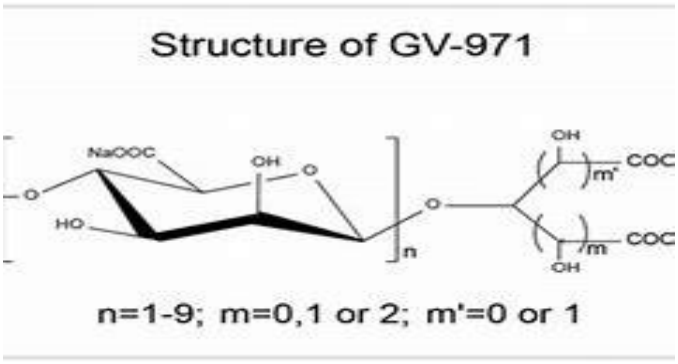

Figure 3. The structure of Sodium Oligomannate[12]

Sodium oligomannate(**Figure 3.)** predominantly targets amyloid precursor protein (APP). Amyloid-beta peptides, recognized for their lipophilicity,reducing copper, zinc, and iron.Aβ42 has higher reductive capacity than Aβ40. Amyloid-beta peptides in cerebrospinal fluid (CSF) interact with lipoproteins such as apolipoproteins E and J, as well as high-density lipoprotein (HDL) particles, preventing metal-accelerated lipoprotein oxidation. Aβ42 may activate brain phagocytes, resulting in inflammation and increased tau aggregation and TPK II-mediated phosphorylation. It also interacts with overexpressed hydroxyacyl-CoA dehydrogenase, generating oxidative stress and neurotoxicity, and binds glypican-1 (GPC1) in lipid rafts, highlighting its multifaceted involvement.APP is a cell surface receptor that regulates neurite formation, adhesion, and axonogenesis; its contact with neighboring cells promotes synaptogenesis and brain connection. Furthermore, APP impacts cell motility and transcription through protein interactions, boosting transcriptional activity by binding APBB1-KAT5 and decreasing Notch signaling via the Numb interaction.Copper-metallated APP can cause neuronal death or intensify effects in vitro through Cu(2+)-mediated low-density lipoprotein oxidation. It also affects neurite outgrowth by binding extracellular matrix components like heparin or collagen types I/IV. As a kinesin I membrane receptor necessary for anterograde cargo transfer to synapses within axons, it maintains copper homeostasis by lowering copper ion levels.The BPTI domain-containing splice isoforms function as protease inhibitors in cultured cortical neurons, where they activate p38 MAPK through an AGER-dependent mechanism that causes mitochondrial dysfunction and amyloid-beta peptide internalization.It provides the Cu(2+) ions needed for GPC1 to generate nitric oxide, which breaks down the heparan sulfate chains on GPC1.Appicans may have an impact on neurite outgrowth by facilitating neural cell attachment to the extracellular matrix [13] .

4.1. Pharmacology of Sodium Oligomannate

The medicine in question is a low-molecular-weight acidic oligosaccharide molecule extracted from marine brown algae. It is a new pharmaceutical product that was independently studied and created in our nation, with its own intellectual property rights. This drug's development has been supported by the National Major Special Project for New Drug Creation and Technology.Mannan capsules have been shown in studies to improve cognitive function by restoring intestinal flora balance, inhibiting abnormal proliferation of specific metabolites produced by intestinal microorganisms, and reducing peripheral and central inflammation. Furthermore, capsules help reduce β-amyloid formation and hyperphosphorylation of tau protein. This unique method of action, which affects the brain-gut axis, serves as a key scientific foundation for a thorough understanding of mannan sodium capsules' clinical effectiveness [14].

4.2. Animal studies

To thoroughly assess the impact of GV-971 on the interplay between microbiota, microglia, and amyloid pathology, two separate studies were carried out at independent research institutes. GV-971 was administered daily to male and female APPPS1-21 mice at dosages of 40, 80, or 160 mg/kg until the amyloid burden peaked at 12 weeks of age, starting at 8 weeks of age, when the amyloid (A) load

became noticeable. Moreover, GV-971 was administered to male and female 5XFAD mice at a daily dose of 100 mg/kg between the ages of 7 and 9 months, when the A burden was near-peak, in order to confirm earlier findings and look into possible sex differences [15].

4.3. Clinical trial

The GRADUATE I and II trials included 985 and 980 people, respectively. The baseline Clinical Dementia Rating-Sum of Boxes score was 3.7 in the GRADUATE I research, but 3.6 in the GRADUATE II experiment. By week 116, participants receiving gantenerumab had a CDR-SB score change of 3.35 from baseline, compared to 3.65 for those receiving placebo in the GRADUATE I trial. This resulted in a difference of -0.31 (95% confidence interval [CI], -0.66 to 0.05; P=0.1).In the GRADUATE II trial, the change from baseline was 2.82 for the gantenerumab group and 3.01 for the placebo group, yielding a difference of -0.19.The difference in amyloid levels measured by positron emission tomography (PET) at week 116 between the gantenerumab and placebo groups was -66.44 centiloids in the GRADUATE I trial and -56.46 centiloids in the GRADUATE II research. Notably, in the first study, 28.0% of gantenerumab patients became amyloid-negative, compared to 26.8% in the second. In both studies, those who received gantenerumab had lower levels of phosphorylated tau 181 in their cerebrospinal fluid (CSF) and higher levels of amyloid beta 42 (A42) than the placebo group.PET showed that the buildup of aggregated tau was comparable across the two treatment groups [16].

5. Summary

When donepezi is taken for 12 or 24 weeks, people with mild, moderate, or severe dementia brought on by Alzheimer's disease see minor improvements in their daily living activities, cognitive performance, and clinician-rated overall clinical status. With few adverse effects, rivastigmine may be useful in the treatment of mild-to-severe svCVD and Alzheimer's disease. The pathogenic features of Alzheimer's disease in the brain, such as intracellular tau tangles and extracellular amyloid plaques, have drawn attention from researchers in recent years. While progress has been made in understanding the pathogenesis of AD, the effectiveness of existing antibody medications targeting Aβ in reducing the burden of AD patients and identifying a basic treatment for the disease is still lacking.In contrast, AD medicines that target neuroinflammation have advanced fast. The new drug Mannata has shown promising results and has great prospects for development.

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