Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/77/2024.LA19856

Research Progress and Future Development Directions of Alzheimer's Disease

Juan Jin

Radley College, Oxfordshire, England, United Kingdom

juan.jin2021@radley.org.uk

Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder marked by the deterioration of neuronal cells, resulting in dementia and a reduction in cognitive abilities and autonomy in daily tasks. AD is a multifactorial disease impacted by numerous factors, including the cholinergic and amyloid hypotheses, advancing age, genetic predispositions, head trauma, vascular disorders, infections, and environmental influences. Present therapies, such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, merely offer symptomatic alleviation without altering the advancement of the disease. Despite decades of research, no curative treatments exist, and numerous clinical trials have failed to demonstrate significant improvements in disease progression. While recent advancements, including the evaluation of drugs like aducanumab, offer hope, the journey toward effective disease-modifying therapies remains ongoing. This review discusses the current state of available treatments, the challenges they face, and future research directions aimed at developing disease-modifying therapies (DMTs) that target abnormal tau protein metabolism, β-amyloid accumulation, inflammatory responses, and other underlying mechanisms.

Keywords: Alzheimer's disease, neurodegeneration, treatment.

1. Introduction

Alzheimer's Disease (AD), ranked as the seventh greatest cause of death globally, is a severe neurological condition that progressively erodes memory and cognitive abilities, ultimately rendering individuals unable to perform even the most basic tasks. Characterized by progressive memory loss, cognitive decline, and behavioural changes, AD affects millions of individuals over the age of 65 [1]. In 2014, the Alzheimer's Association projected that 6.9 million Americans aged 65 and older were living with Alzheimer's disease. The ageing global population is expected to result in a doubling of annual Alzheimer's cases by 2050, hence intensifying the strain on healthcare systems and families. The danger of Alzheimer's disease extends beyond the decline in cognitive abilities; it encompasses the gradual loss of independence, severe impairment in daily functioning, and significant emotional distress for both patients and caregivers. The disease impacts not only individuals but also the broader community, creating substantial social and economic challenges. With the rising incidence of Alzheimer's disease, the need for direct carers is projected to exceed 1 million extra personnel between 2021 and 2031, representing the highest increase in workforce for any single occupation in the United States. Alongside the social challenges, AD also causes severe economic burden; in 2024, the total payment for all individuals with AD is estimated at $360 billion. These alarming figures underscore the importance of

DOI: 10.54254/2753-8818/77/2024.LA19856

effective treatment to alleviate not only the death of Alzheimer's disease but also its growing economic and societal impact. The Centres for Disease Control and Prevention (CDC) reported that 119,399 individuals died of Alzheimer's disease in 2021 [2]. Current treatment options only aim to manage symptoms rather than stop or reverse the disease process. Despite advances in medical research, existing therapies provide only temporary relief and cannot cure or alter the progression of AD. Furthermore, as the disease progresses, the efficacy of these treatments declines, highlighting the critical need for ongoing research and development in this field.

This paper will discuss the current Alzheimer's treatments, detailing the various approaches available, their benefits, and their limitations. By examining the state of current therapies and identifying limitations in them, this discussion aims to provide insight into the future directions for research against Alzheimer's disease.

2. What is AD

AD is a slowly progressing neurological disorder that predominantly impacts memory, cognition, and behaviour. The initial phase, marked by early pathological alterations in the cortex and hippocampus, presents symptoms like memory impairment and cognitive challenges that progressively deteriorate over time. As the disease disseminates throughout the cerebral cortex, damage commences in regions of the brain responsible for language, reasoning, conscious cognition, and sensory processing. Furthermore, patients might experience hallucinations, delusions, and paranoia. In the late stage, where the disease spreads throughout the entire cortical region with significant accumulation of neuritic plaques and neurofibrillary tangles, the brain tissue undergoes substantial atrophy, ultimately resulting in a loss of physical functions [1,3].

The cause of Alzheimer's disease is not fully understood yet; however, it is considered a multifactorial disease associated with several risk factors, including increasing age, genetic factors, head injuries, vascular disease, infections, and environmental factors [3].

2.1. Pathology of AD

A key pathogenic characteristic of Alzheimer's disease is the aggregation of amyloid β and the hyperphosphorylation of tau protein. Amyloid β is a fragment of a larger protein, and when they accumulate together, they can produce a toxin effect on neurons that disrupts their communication between brain cells, resulting in synaptic and neuronal loss. Additionally, amyloid-β (Aβ) unnaturally aggregates with Aβ40 and Aβ42—two byproducts of amyloid precursor protein (APP) metabolism—resulting in the formation of amyloid plaques, which are extracellular deposits [4]. The presence of amyloid plaques in the brain is particularly dangerous because it not only impairs neuron communication but also triggers inflammatory responses and oxidative stress, accelerating widespread neuronal damage and cognitive decline [5,6].

Tau is a protein that is produced in the neurone. Normally, tau helps stabilize microtubules in the cytoskeleton, which are essential for maintaining the structure and function of neurons. However, in Alzheimer's patients, through hyperphosphorylation, tau detaches from the microtubules and clumps together to form neurofibrillary tangles. NFTs develop in Alzheimer's disease patients due to elevated tau phosphorylation and intracellular tau aggregation, resulting from the breakdown of the balance between tau kinase and phosphatase activity [7]. As the NFT accumulates, they cause neurons to malfunction and die by abnormally interacting with the cellular proteins, causing them to be unable to function normally. Unlike amyloid plaques, which affect the space between neurons, tau tangles directly impact the internal function of the neurons, contributing to brain atrophy and further accelerating the decline in brain function [5,6].

DOI: 10.54254/2753-8818/77/2024.LA19856

3. Current Treatments of AD

3.1. Cholinesterase Inhibitors

The cholinergic hypothesis is the earliest theory proposed to explain the cognitive decline in AD. During the 1970s, it was believed that deficiencies in neocortical and presynaptic cholinergic function were associated with the enzyme choline acetyltransferase (ChAT), which facilitates the synthesis of acetylcholine (ACh). Acetylcholine (ACh) is found in both the peripheral and central nervous systems and is linked to learning capabilities, cognitive skills, and memory. Consequently, due to ACh's critical involvement in cognitive function, a cholinergic hypothesis for AD was postulated. These actions are executed by basal forebrain cholinergic neurones (BFCN), which are reduced in AD patients due to neuronal degeneration, hence reinforcing the hypothesis that AD is associated with ACh. This theory is further corroborated by brain tissue research of Alzheimer's disease patients, which reveals neurodegeneration characterised by observable deficiencies in cholinergic neurones and reduced levels of acetylcholine. The presence of Aβplaques has also been shown to impair cholinergic synapses, further disrupting neurotransmission. As a result, cholinesterase inhibitors (ChEIs) were developed as a therapeutic strategy to slow the breakdown of ACh and restore cholinergic function, thereby improving cognitive performance in AD patients [3,5,8,9].

Tacrine was the first cholinesterase inhibitor approved by the FDA in 1993 for the treatment of AD. Tacrine functions by hindering the metabolism of acetylcholine, thus extending its activity and elevating its levels in the cerebral cortex. However, due to its significant side effects, including hepatotoxicity, gastrointestinal disturbances, and a high discontinuation rate, it is no longer widely used. While tacrine was a pioneering AD treatment, it has been largely replaced by newer, safer cholinesterase inhibitors like donepezil, rivastigmine, and galantamine [10,11].

Donepezil is among the most often utilised cholinesterase inhibitors for the symptomatic management of Alzheimer’s disease. Approved by the FDA in 1996, this second-generation medication functions by reversibly binding to acetylcholinesterase (AChE) and inhibiting acetylcholine hydrolysis, resulting in elevated acetylcholine levels. Donepezil has demonstrated efficacy in enhancing cognitive function and behaviour in individuals with mild to moderate Alzheimer's disease. Although generally well-tolerated, it may induce moderate gastrointestinal adverse effects, including nausea, vomiting, and diarrhoea. Moreover, it is expected that one-third of patients would exhibit no discernible outcomes, while an equivalent proportion may experience adverse effects, leading to decreased tolerance and disqualification of this medication. Notably, donepezil does not alter the progression of the disease but is effective in managing symptoms for a period of time. It remains a leading therapeutic option in AD due to its efficacy in enhancing memory and attention [3,5,12,13].

Rivastigmine, a carbamate-based pseudo-irreversible inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), received FDA approval in 2000. It preferentially inhibits cholinesterase activity in the central nervous system (CNS), as shown by reductions in cerebrospinal fluid cholinesterase activity. Rivastigmine is available in both capsule and solution forms for oral administration. It is unlikely to cause significant pharmacokinetic drug-drug interactions due to its low protein binding and the fact that it is not metabolized by the hepatic cytochrome P450 system, unlike other cholinesterase inhibitors such as donepezil and galantamine. Nonetheless, it induces gastrointestinal adverse effects, including nausea, vomiting, and diarrhoea. In clinical trials, nausea occurred in 17–48% of patients, vomiting in 16–27%, and diarrhea in 11–17%. Rivastigmine has shown efficacy in both short- and long-term treatment for mild to moderate AD, offering symptomatic relief and delaying cognitive decline. While gastrointestinal side effects remain a challenge, careful dosing and transdermal patch formulations may mitigate these issues [3,5,14].

Galantamine is another first-line treatment for mild to moderate Alzheimer’s disease, approved by the FDA in 2001. It possesses a dual method of action: it inhibits acetylcholinesterase and allosterically binds to the α-subunit of nicotinic acetylcholine receptors, hence increasing cholinergic neurotransmission. In clinical trials, galantamine (16–24 mg/day) markedly enhanced cognitive and overall symptoms in patients with mild to moderate AD over a duration of 3 to 6 months. It also

DOI: 10.54254/2753-8818/77/2024.LA19856

enhanced daily living activities and reduced the need for caregiver assistance. Over a 12-month period, galantamine (24 mg/day) impeded disease progression, maintaining cognitive abilities and daily functioning. The medication is typically well taken, with prevalent side effects such as nausea and vomiting being predominantly minor, temporary, and alleviated by modest dose escalations [3,5,15].

The cholinergic hypothesis of Alzheimer's disease emphasizes the crucial role of acetylcholine in cognitive functions and how its decline, due to cholinergic neuron degeneration, contributes to AD symptoms. Cholinesterase inhibitors like Donepezil, Rivastigmine, and Galantamine have emerged as symptomatic treatments, offering temporary cognitive improvements by boosting acetylcholine levels. While these drugs have shown efficacy in managing mild to moderate AD symptoms, their impact on disease progression remains limited. Gastrointestinal side effects are common, underscoring the need for careful dosing and further therapeutic advancements.

3.2. Memantine

Memantine, approved by the FDA in 2003, is a non-competitive, low-affinity antagonist of N-methyl-D-aspartate (NMDA) receptors, essential for regulating synaptic plasticity, learning, and memory. Alzheimer's disease is associated with excessive NMDA receptor activity leading to pathological Ca^{2+} influx, excitotoxicity, and neuronal damage. Memantine selectively blocks overactive NMDA receptors, reducing neurodegeneration while preserving normal synaptic transmission. This unique mechanism allows memantine to mitigate excitotoxicity without disrupting essential cognitive processes. Often used alongside acetylcholinesterase inhibitors, memantine's neuroprotective effect helps alleviate moderate to severe Alzheimer's symptoms. Clinical trials demonstrate that memantine improves cognition, daily functioning, and behavioural symptoms in AD patients. Memantine has a generally favourable safety profile, with adverse effects like dizziness, headache, confusion, and somnolence being rare. Though its monotherapy efficacy is moderate, combination therapy with donepezil enhances clinical outcomes, slowing cognitive decline and improving patient quality of life [10,16].

3.3. Aducanumab

Aducanumab is an innovative monoclonal antibody that received FDA approval in June 2021 for the treatment of Alzheimer's disease, becoming the first medication specifically aimed at Aβ aggregates. It operates by augmenting microglial phagocytosis, resulting in the elimination of Aβ plaques and perhaps boosting cognitive function in individuals with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD). Despite its promise, aducanumab's approval was met with controversy due to inconsistent results from Phase 3 trials and the realization that Aβ reduction does not necessarily correlate with improved neuropsychological outcomes. Furthermore, this amyloid clearance is linked to a notable side effect—amyloid-related imaging abnormalities (ARIA). These anomalies encompass ARIA-H, marked by hemosiderin accumulation (including superficial siderosis and microhemorrhages), and ARIA-E, which presents as brain edema. In clinical trials, 41% of individuals treated with aducanumab at the target dose of 10 mg/kg had ARIA, in contrast to merely 10% of those receiving placebo. Furthermore, those possessing the APOE4 gene had an increased prevalence of ARIA-E. Although ARIA generally diminishes over time, particularly between weeks 12 and 20, severe instances of ARIA-H required permanent cessation of the medication. Furthermore, tau accumulation has emerged as a stronger predictor of cognitive decline, raising questions about the drug's efficacy. While some patients may experience side effects, including amyloid-related ARIA, aducanumab represents a significant step in AD treatment. However, the European Medicines Agency has advised against its marketing authorization, underscoring the need for further research to fully understand its benefits and risks in managing this complex disease [5,10,17].

4. Combination Therapy for Alzheimer's Disease

Combination therapy for Alzheimer's disease seeks to improve therapeutic results by addressing various mechanisms implicated in disease progression. The two primary drug classes used in this approach are acetylcholinesterase inhibitors (AChEI), such as donepezil, and NMDA receptor antagonists, like

DOI: 10.54254/2753-8818/77/2024.LA19856

memantine. AChEIs aim to boost cholinergic signaling, addressing the cognitive deficits associated with AD, while memantine mitigates glutamate-induced excitotoxicity. Given that Alzheimer's disease is a multifactorial disorder, the combination of treatment drugs may be more efficacious than monotherapy [18].

4.1. Combination of Galantamine and Memantine

Combination therapy using galantamine and memantine is based on the synergistic effects of both drugs in combating Alzheimer's disease pathology by targeting different neural pathways. Galantamine, primarily known for its acetylcholinesterase inhibition, also activates nicotinic acetylcholine receptors, protecting neurons from glutamate-induced excitotoxicity. Memantine, as an NMDA receptor antagonist, prevents excessive Ca^{2+} influx linked to neurodegeneration. The study by Loped et al [19]. has shown that these drugs, when used in combination at subtherapeutic doses, enhance neuroprotection. It is posited that complete neuroprotection may be attained with the combination of subactive quantities of memantine and galantamine. This dual-action approach helps alleviate neuronal damage and improves cognitive function more effectively than monotherapy. Experimental designs have facilitated the creation of hybrid compounds that integrate these pathways by connecting two therapeutic molecules with a variable-length polymethylene linker, so providing a more holistic therapy approach for Alzheimer's disease [10,18].

4.2. Combination of Memantine and Nitroglycerin

The combination of memantine and nitroglycerin has emerged as a promising strategy for enhancing the therapeutic efficacy of Alzheimer's disease treatments. By linking memantine with a pharmacophore derived from nitroglycerin, specifically the nitrooxy moiety (–ONO_2), researchers have developed second-generation memantine analogs, such as nitromemantine. This innovative approach aims to provide memantine with significant disease-modifying effects, potentially addressing both cognitive deficits and neurodegenerative processes associated with Alzheimer's. In preclinical studies involving triple transgenic AD mouse models, nitromemantine demonstrated superior efficacy compared to standard memantine, notably improving synaptic density and cognitive function. These findings suggest that the addition of the nitrooxy unit not only enhances neuroprotection but also restores synaptic connections, raising hopes for its application in clinical settings. Furthermore, nitromemantine has shown no adverse effects on blood pressure. As clinical trials for nitromemantine advance, the potential for this combination therapy to significantly alter the course of Alzheimer's disease is an exciting development in the field [10,18].

4.3. Combination of Donepezil and Clioquinol

The combination of donepezil and clioquinol represents a strategic advancement in the treatment of Alzheimer's disease, leveraging the unique pharmacological properties of both compounds. Donepezil, an established acetylcholinesterase inhibitor, enhances cholinergic signaling, which is crucial for cognitive function. Clioquinol, a metal chelator, targets the elevated levels of zinc and copper found in amyloid plaques, which are linked to neuroinflammation and amyloid toxicity. A series of hybrid compounds has been developed by combining the pharmacophore of donepezil with the metal-chelating characteristics of clioquinol. This approach aims to produce smaller hybrid compounds with improved pharmacokinetic properties compared to traditional linking strategies, which often result in larger molecules with suboptimal characteristics. The newly designed hybrids exhibit a dual mechanism of action: they inhibit amyloid-beta aggregation while simultaneously scavenging free radicals and chelating metal ions, thus mitigating oxidative stress and metal-induced neurotoxicity. Research demonstrates that these hybrids proficiently inhibit the self-aggregation of amyloid-beta and preferentially engage human butyrylcholinesterase (BuChE), hence augmenting their therapeutic efficacy. Compounds such as 7-((4-(2-methoxybenzyl))piperazin-1-yl)methyl)-8-hydroxyquinoline exhibit significant in vitro antioxidant activities and advantageous blood-brain barrier permeability. The combination of donepezil and clioquinol, therefore, not only aims to improve cognitive function but also

DOI: 10.54254/2753-8818/77/2024.LA19856

addresses the neurotoxic environment characteristic of Alzheimer's disease, providing a comprehensive treatment strategy that could significantly alter disease progression [18,20].

5. Non-pharmacological Treatment of AD

Non-pharmacological treatments for AD play a crucial role in enhancing patients' quality of life and potentially mitigating disease progression. These interventions encompass a variety of lifestyle measures, including physical activity, social engagement, and music therapy. Consistent physical exercise has demonstrated efficacy in enhancing cognitive function and decelerating the advancement of cognitive decline in patients with moderate cognitive impairment (MCI) and AD. It stimulates neurogenesis, augments cerebral blood flow, and facilitates the release of brain-derived neurotrophic factor (BDNF), essential for memory and learning. Similarly, maintaining strong social connections is essential, as social isolation has been linked to accelerated cognitive decline and increased risk of neurological diseases. Engaging in social activities can improve cognitive performance and may help delay the onset of AD symptoms. Music therapy has emerged as another promising approach, demonstrating potential benefits in memory, emotion, and overall well-being for dementia patients. This therapy involves both active participation, such as singing and dancing, and passive experiences, like listening to music, creating a therapeutic environment that can alleviate anxiety and improve mood. Collectively, these non-pharmacological strategies highlight the importance of a holistic approach in managing Alzheimer's disease, focusing not only on cognitive health but also on emotional and social well-being [5,10].

6. Limitations

Current therapies for AD face several significant limitations, despite their advancements. Cholinesterase inhibitors like donepezil, rivastigmine, and galantamine primarily target symptoms by increasing acetylcholine levels, but they do not modify the underlying disease progression. About one-third of patients experience no noticeable benefits, and a similar proportion may suffer from gastrointestinal side effects, limiting long-term use and patient adherence. Memantine, while offering some neuroprotective effects, has moderate efficacy when used alone and is often used in combination with cholinesterase inhibitors to enhance outcomes. However, its impact on cognitive decline remains modest. The recent introduction of aducanumab, targeting amyloid-beta aggregates, has sparked significant controversy owing to conflicting clinical trial outcomes and safety concerns, particularly about amyloid-related imaging abnormalities (ARIA). Furthermore, the relationship between amyloid clearance and cognitive improvement is not fully understood, raising doubts about its overall effectiveness. Overall, while these therapies provide some symptomatic relief, there is a pressing need for novel approaches that address the multifactorial nature of AD and offer more definitive modifications to its progression.

7. Future development directions of AD

Looking ahead, future development directions must focus on more holistic and innovative approaches. Promising avenues of research include targeting pathological features such as amyloid-beta and hyperphosphorylated tau proteins through disease-modifying therapies (DMTs). Ongoing clinical trials for agents like aducanumab, gantenerumab, and crenezumab aim to assess their efficacy in altering the disease trajectory. Furthermore, emerging molecules such as heat shock proteins and vacuolar sorting protein 35 (VPS35) show potential in facilitating optimal protein activity within cells, thereby providing new therapeutic strategies for neurodegenerative disorders. Furthermore, natural extracts from traditional medicine show potential in addressing multiple mechanisms involved in AD [3].

8. Conclusion

AD remains one of the most pressing challenges in modern healthcare, affecting millions and imposing significant social and economic burdens. While current treatments, including cholinesterase inhibitors and memantine, offer symptomatic relief, they do not halt the disease's progression. The emergence of aducanumab marks a significant step in targeting amyloid-beta aggregates; however, its mixed clinical

DOI: 10.54254/2753-8818/77/2024.LA19856

outcomes and safety concerns underscore the complexity of AD treatment. The success of future therapies will depend on their early implementation, continuous patient monitoring using biomarkers, and the exploration of combination therapies targeting both amyloid and tau pathologies. A concerted effort to design potent, selective, and effective drugs is critical to improving outcomes for patients with AD and those at risk of developing the disease.

References

[1] Alzheimer's disease fact sheet | National Institute on Aging. (2023). Available at: https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet (Accessed: 21 September 2024).
[2] 2024 alzheimer's disease facts and figures. (2024). Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf (Accessed: 21 September 2024).
[3] Breijyeh, Zeinab, and Rafik Karaman. (2020). "Comprehensive Review on Alzheimer's Disease: Causes and Treatment" *Molecules 25*, no. 24: 5789. https://doi.org/10.3390/molecules25245789
[4] Lane, C.A., Hardy, J. and Schott, J.M. (2018). Alzheimer's disease. *Eur J Neurol, 25*: 59-70. https://doi.org/10.1111/ene.13439
[5] Doroszkiewicz, Julia, and Barbara Mroczko. (2022). "New Possibilities in the Therapeutic Approach to Alzheimer's Disease" *International Journal of Molecular Sciences 23*, no. 16: 8902. https://doi.org/10.3390/ijms23168902
[6] Alzheimer's disease. (2024). Mayo Clinic. Available at: https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447#:~:text=Alzheimer's%20disease%20causes%20the%20brain, a%20person's%20ability%20to%20function (Accessed: 21 September 2024).
[7] Ludovic Martin, Xenia Latypova, Cornelia M. Wilson, Amandine Magnaudeix, Marie-Laure Perrin, Catherine Yardin, and Faraj Terro. (2013). "Tau protein kinases: Involvement in Alzheimer's disease" *Ageing Research Reviews*, *12*, (1). https://doi.org/10.1016/j.arr.2012.06.003
[8] Xuan Gu and Xiaoying Wang. (2021). "An overview of recent analysis and detection of acetylcholine" *Analytical Biochemistry, 632:* 114381. https://doi.org/10.1016/j.ab.2021.114381
[9] Bowen, D. M. , Smith, C. B. , Pamela, W. , & Davison, A. N. . (1976). Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. *Brain A Journal of Neurology*(3), 459-96. https://doi.org/10.1093/brain/99.3.459.
[10] Rouchan Ali, Ghanshyam Das Gupta, and Pooja A. Chawla. (2022). "Aducanumab: A new hope in Alzheimer's disease" *Health Sciences Review, 4*. https://doi.org/10.1016/j.hsr.2022.100039
[11] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Tacrine. [Updated 2020 Jan 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547868/
[12] Kumar A, Gupta V, Sharma S. Donepezil. [Updated 2023 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513257/
[13] Robert Briggs, Sean P Kennelly, and Desmond O'Neill. (2016). "Drug treatments in Alzheimer's disease" *Clinical Medicine, 16*, 3. https://doi.org/10.7861/clinmedicine.16-3-247
[14] Annicchiarico, R., Federici, A., Pettenati, C., & Caltagirone, C. (2007). Rivastigmine in Alzheimer's disease: Cognitive function and quality of life. *Therapeutics and Clinical Risk Management, 3*(6), 1113–1123. https://doi.org/10.2147/tcrm.s12160487
[15] Scott, L.J., Goa, K.L. Galantamine. Drugs 60, 1095–1122 (2000). https://doi.org/10.2165/00003495-200060050-00008

DOI: 10.54254/2753-8818/77/2024.LA19856

[16] Kuns B, Rosani A, Patel P, et al. Memantine. [Updated 2024 Jan 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500025/

[17] Vaz, M., Silva, V., Monteiro, C., & Silvestre, S. (2022). Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities. *Clinical Interventions in Aging, 17*, 797–810. https://doi.org/10.2147/CIA.S325026

[18] Kabir MT, Uddin MS, Mamun AA, Jeandet P, Aleya L, Mansouri RA, Ashraf GM, Mathew B, Bin-Jumah MN, Abdel-Daim MM. Combination Drug Therapy for the Management of Alzheimer's Disease. *Int J Mol Sci. 21*(9):3272. doi: 10.3390/ijms21093272. PMID: 32380758; PMCID: PMC7246721.

[19] Lopes, J.P., Tarozzo, G., Reggiani, A., Piomelli, D. and Cavalli, A. (2013), Galantamine potentiates the neuroprotective effect of memantine against NMDA-induced excitotoxicity. *Brain Behav, 3*: 67-74. https://doi.org/10.1002/brb3.118

[20] F. Prati, C. Bergamini, R. Fato, O. Soukup, J. Korabecny, V. Andrisano, M. Bartolini, M. L. Bolognesi, *ChemMedChem.11*(12):1284-95. https://doi.org/10.1002/cmdc.201600014