



## Combination Of Riluzole And Rivastigmine- A Potential Treatment Strategy For Alzheimer's Disease

Chintha Narendar<sup>1</sup>, M Tharani<sup>2</sup>, Gaddam Narasimha Rao<sup>2</sup>, M Anvesh Raj<sup>3</sup>, Antony Justin<sup>1\*</sup>

<sup>1,2</sup>Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India.

<sup>3</sup>Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India.

\*Corresponding author: Antony Justin, Associate Professor, Department of Pharmacology, JSS College of Pharmacy Ooty, Tamilnadu, 643001, Email: justin@jssuni.edu.in

Submitted: 10 January 2023; Accepted: 22 February 2023; Published: 07 March 2023

### ABSTRACT

To fulfill clinical needs, it is essential to deploy viable treatment techniques for Alzheimer's disease (AD). The development of potential therapeutic drugs for the treatment of Alzheimer's disease in the early stages and the optimization of symptomatic treatment are top priorities in AD research. Recently multitarget therapies are gaining a lot of interest due to their potential advantages. The current review aims to review the advantages of combined targeting of Cholinesterase inhibitors (ChEIs) and N-methyl D-aspartate (NMDA) antagonists in the treatment of AD. In order to evaluate the all-possible aspects of ChEIs and NMDA antagonists in the treatment of AD, we have examined documentation available in published literature. Recently, Riluzole has been approved for amyotrophic lateral sclerosis (ALS), and rivastigmine for Alzheimer's disease. A recent study suggested that Riluzole may show therapeutic benefits in the treatment of AD. As, Rivastigmine is an existing therapy for mild to moderate AD, drugs that act for severe AD are necessary. So, combination therapy (CT) with Riluzole and rivastigmine may act as a potential treatment strategy for AD is beneficial. When compared with monotherapy, the combination approach simplifies the treatment regimen and increases patient compliance. For sufferers with excessive AD, CT with ChEIs and NMDA antagonists seems to be the simplest and most powerful therapy.

**Keywords:** *Alzheimer's disease, Riluzole, Rivastigmine, Combination therapy, neurodegenerative disease*

### INTRODUCTION

Neurodegeneration is a disease in which nerve function is lost over time, this causes cognitive decline, memory loss, and ataxia in various forms. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) all have these characteristics. Neurodegenerative diseases are a significant economic and social danger to our civilization, particularly in low-

and middle-income nations. Neurodegenerative disease could be a state of failure of the formation of the nerve cell at the side of the death of neurons within the human brain [1]. The core pathological mechanism is the deposition and aggregation of misfolded proteins within the brain that results in progressive neurodegenerative illness [2].

Though the region yet as cellular distribution and deposition of the collective proteins could vary from disease to disease, there are some links between the illness within the pathways of supermolecule aggregation. Most neurodegenerative illnesses with idiopathic etiologic effects in elderly patients. Genetic predisposition, environmental factors, and aging are the riskiest factors of AD [3].

AD is the most common cause of severe neurocognitive impairment. Aloysius Alzheimer first discovered AD in a 51-year-old patient in 1907. He discovered senile plaques, neurofibrillary tangles, and amyloid angiopathy on autopsy, all of which are AD markers [4]. In 2018, there were around 5.7 million persons in the United States living with AD; by 2025, this number is expected to rise by over 30%, to 7.1 million, and by 2050, to 13.8 million. It is estimated that 24 million individuals are impacted globally. Because both developed and developing nations are aging, the frequency is expected to increase every 20 years until 2040.

The predicted increase as a result of societal aging is large, and it will be an expensive public health burden in the coming years. AD is the sixth largest cause of mortality in the United States, according to the Centres for Disease Control and Prevention (CDC) [5]. According to the 2010, Dementia India Report by the Indian Society for Alzheimer's disease and Related Diseases (ARDSI), approximately 3.7 million Indians suffered from dementia in 2010, and this number is expected to rise to 7.6 million by 2030.

### ***Potential Benefits of Combination***

When it comes to treating Alzheimer's disease, monotherapy has a number of disadvantages. Furthermore, it is unlikely that monotherapy focused on a single molecular target will alter AD etiology sufficiently to affect the disease progression. But high doses of monotherapy are more effective, and also side effects are associated which are likely to be severe. This notion is particularly applicable to ChEIs. Their tolerability decreases as their efficacy rises in a dose-dependent manner. In the context of a

successful pharmacological strategy, treatment with a combination of drugs with unique mechanisms of action may be more helpful than monotherapy. Combination therapy (CT) may potentially improve the efficacy of medications by increasing activities that are synergistic or additive. As a result, CT tolerance and safety have increased, and lesser doses of CT may be employed. CT exhibits neuroprotective properties, extending the alleviation of symptoms and delaying the onset of disease [5].

The more predictable pharmacokinetic and pharmacodynamic relationship of the components of a single medicine, the possibility that one moiety may improve the bioavailability of the second entity, the greater efficacy against advanced-stage diseases, the lower toxicities, the simultaneous presence of the chemical entities in multiple tissues, and improved patient compliance are all advantages of multi-target drugs over drug combinations.

### ***Pathophysiology of AD***

The neuropathology of AD is defined by extracellular amyloid plaques, intracellular neurofibrillary tangles, and nerve cell death [6-8]. Amyloid plaques are generated when the amyloid protein precursor (APP) is broken by  $\beta$ -secretase (BACE 1), which is then followed by  $\gamma$ -secretase, resulting in Amyloid  $\beta$  ( $A\beta$ ).  $A\beta$  Monomers are formed over time from oligomers, fibrils, and insoluble amyloid plaques [6].

Neurofibrillary tangles, another signature protein aggregate of AD, are made up of hyperphosphorylated tau protein. When tau is hyperphosphorylated, it creates "tangles" of paired helical filaments, which aid microtubule stability in normal conditions [7]. According to the amyloid cascade hypothesis,  $A\beta$  buildup affects synaptic and neuronal function, leading to the formation of neurofibrillary tangles and neuronal death, as well as further degradation of neurotransmitter function [6]. Because of cholinergic neuron death in the basal forebrain, cholinergic insufficiency is hypothesized to contribute to short-term memory loss in AD [8].

## **Drug treatment of AD**

### **Anti-A $\beta$ therapy**

Amyloid peptides play a key role in the pathogenesis of Alzheimer's disease. Anti-amyloid therapy involves the use of drugs with different mechanisms of action: (i) they enhance A $\beta$  clearance; (ii) prevention of A $\beta$  production; or (iii) inhibit A $\beta$  accumulation [9]. Numerous studies have found that high levels of A $\beta$  cause neuronal damage. A $\beta$  production is associated with synaptic dysfunction, intraneuronal fibrillary entanglements, and neuronal death. [10]. Neurites may shorten and neurons may denature as a result of the deposited A $\beta$ . A $\beta$  peptides affect AChE levels; Thus, A $\beta$  responsible for the increase in AChE around the plaques. However, the improvement in AChE associated with NFT has been generally neglected [11]. A $\beta$  may disrupt calcium channels in the cell membrane, resulting in increased Ca<sup>2+</sup> influx and calcium disequilibrium. As a result, anti-A $\beta$  medications may be the most effective AD treatment.

### **Acetylcholinesterase inhibitors (AChEIs)**

#### **Tacrine**

Tacrine was the first Alzheimer's drug to be approved by the FDA in the United States (tetrahydro amino acridine; Cognex-Warner-Lambert) [12]. The drug (dual inhibitor) inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), lowering acetylcholine metabolism and increasing acetylcholine availability for muscarinic receptor binding. As AD progresses, AChE levels decrease but BChE levels remain constant or rise, which could explain why dual cholinesterase inhibitors are more effective [13]. In clinical trials, tacrine has had mixed results in terms of efficacy [14].

Despite the fact that some studies showed a statistically significant decline in cognition, the drug was withdrawn in 2013 due to serious adverse events [15]. The most common of which were gastrointestinal toxicity and, less commonly, hepatotoxicity (high transaminase levels), both of which could result in death [16]. The requirement to take tacrine three times a day, which often resulted in poor adherence, as well

as the requirement to check liver enzymes, assisted in tacrine's demise.

#### **Donepezil**

Donepezil (Aricept Eisai/Pfizer) was the FDA's second cholinesterase inhibitor approval. By increasing the amount of acetylcholine in the synaptic cleft [17]. Donepezil acts as a highly selective, reversible, centrally-acting acetylcholinesterase inhibitor. This method of action is supported by AD and the cholinergic hypothesis, which claims that increasing acetylcholine levels improve neuronal function [18].

In a 2017 meta-analysis, Blanco Silvente et al. discovered that donepezil was more effective than galantamine or rivastigmine in treating common symptoms of AD [19]. The most common donepezil side effects are related to its mechanism of action and increase in cholinergic activity. Nausea, vomiting, diarrhea, and abdominal cramping have been reported as GI side effects [17,18]. Sleep disturbances have been reported as well as relatively unusual cardiac AEs such as bradycardia and QTc prolongation [20].

#### **Rivastigmine**

Rivastigmine (Exelon Novartis Pharmaceuticals Corporation) is a dual AChE and BChE inhibitor that was approved by the FDA in 2000 for the treatment of mild AD dementia and again in 2006 for the treatment of moderate-to-severe Parkinson's disease dementia [21]. Dual inhibition may have additional benefits due to the presence of the latter in subcortical regions associated with executive processes and attention [22].

Despite these advantages, rivastigmine was associated with the highest incidence of adverse events and the highest rate of discontinuation when compared to other cholinesterase inhibitors [19,22]. Regardless, there has been no evidence of a disease-modifying effect in randomized controlled trials [23]. Rivastigmine has a significantly higher death rate when compared to other ChEIs [24]. This is due to the fact that the

old rivastigmine patch is no longer being removed prior to the installation of the new one, particularly when the preliminary loading dosage patch is involved. Patch poisoning can cause nausea, vomiting, hypersalivation, miosis, fasciculations, and severe bradycardia.

### ***Galantamine***

Galantamine (Janssen Pharmaceuticals), also known as Razadyne, is an AChE selective reversible inhibitor that was first approved in the United States in 2000 as a therapy for AD [25]. The drug inhibits acetylcholinesterase reversibly and competitively, improving cholinergic tone and increasing ACh activity at the synapse [26]. Users report an increase in central cholinergic tone as a result of the substance's inherent ability to cross the blood-brain barrier [27].

Galantamine is also an allosteric modulator of nicotinic acetylcholine receptors (nAChRs), increasing their expression and interest in critical cholinergic neurotransmission in addition to blocking AChE [28]. This action aids in the partial repair of septohippocampal cholinergic pathway deficits, which are common in AD patients [29]. Patients treated with AD medication demonstrated improved cognitive performance and a significant delay in the development of disease-related behavioral problems [30]. Galantamine is primarily metabolized in the liver by CYP 450 isoenzymes, particularly CYP 2D6 / 3A4, and it has a low risk of drug interactions due to multiple metabolic pathways [26].

### ***NMDA receptor antagonist***

Synaptic dysfunction may be caused by a disruption in synaptic Ca<sup>2+</sup> handling caused by glutamate receptor overactivation, specifically the N-methyl D-aspartate receptors (NMDAR) [31]. In the brain, the excitatory neurotransmitter glutamate acts on both ionotropic and metabotropic glutamate receptors. The ionotropic glutamate receptors (iGluR) amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA), kainate receptors, and NMDAR receptors are three subfamilies that are important for fast neuronal transmission at the excitatory synapse [32]. Excitotoxicity is caused by excessive glutamatergic signaling [33]. Aside

from immediate effects, many studies suggest that glutamate excitotoxicity contributes to slow-moving neurodegeneration [34]. The primary cause of toxicity is excessive Ca<sup>2+</sup> entry particularly through NMDARs because NMDARs have significantly higher calcium ion permeability than other iGluRs [35]. Synaptic transmission and synaptic plasticity are thought to be the underlying causes of learning and memory deficits, and the NMDAR is essential for both. It is also necessary for the development and function of the nervous system, as well as for the prevention of neurotoxicity. Recently, NMDAR activity has been linked to synaptic disruption in AD [36]. Abnormal Ca<sup>2+</sup> signaling causes gradual loss of synaptic function and, eventually, nerve cell death, which is clinically consistent with the progressive decline of cognitive function/memory and the development of pathological brain morphology seen in AD patients. As a result, NMDAR antagonists (for example, memantine) are used as an asymptomatic and neuroprotective therapy for AD [37].

### ***Memantine***

Memantine is a non-competitive NMDAR antagonist approved for the treatment of moderate to severe Alzheimer's disease symptoms. It is frequently used to relieve symptoms and improve the quality of life in Alzheimer's disease, despite the fact that it does not alleviate acute hippocampal excitation or complete brain atrophy [38]. It is hypothesized that memantine protects cells by reducing excitotoxicity caused by NMDA glutamate receptor overactivation during synaptic transmission. Memantine reduces Ca<sup>2+</sup> influx and improves cognition and behavior by binding to NMDA receptors, which prevents overstimulation [39]. Despite the fact that memantine was only approved by the FDA for the more severe forms of Alzheimer's disease, it was found to be effective in phase III trials for both moderate-to-severe, and mild-to-moderate cases [40]. Nonetheless, the overall evidence suggests that clinically significant effects on cognition, mood and daily activity performance are found primarily in more severe forms of AD [41].

Because cells require some NMDA activity to function properly, it is critical not to completely inhibit all glutamate-mediated synaptic transmission. Memantine meets this criterion because it specifically inhibits excessive stimulation [42]. NMDA antagonists, such as memantine, are commonly thought to be neuroprotective, but they have also been shown in humans to be neurotoxic, causing memory loss, cell death, and even psychotic episodes [43]. Memantine's neurotoxicity may be exacerbated by AChEIs. According to recent research, combining other NMDA antagonists and AChEIs may not cause such side effects, and such combinations may reduce cognitive decline more effectively than either memantine or AChEIs alone [44].

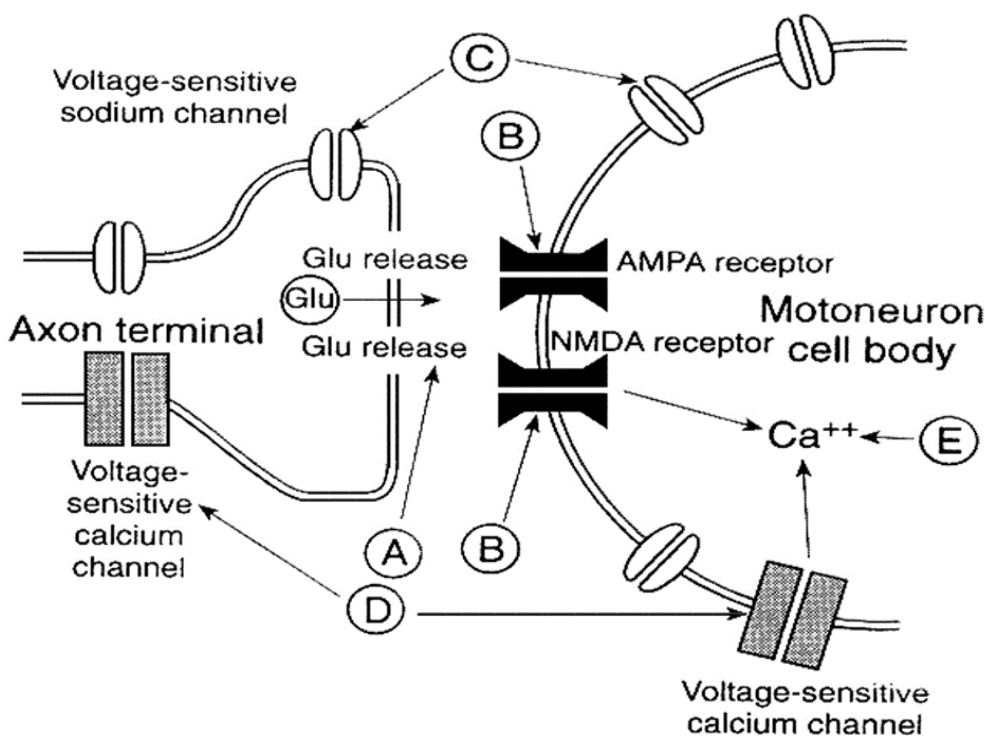
**Riluzole: mechanism of action**

Riluzole could be a neuroprotective drug during which the mechanism of action is unknown. It will block the glutamatergic somatic cell transmission in the brain by inhibiting the discharge of aminoalkanoic acid from CNS. By inhibiting the NMDA receptor and activating a G-protein-dependent signal transduction

cascade, this method prevents amino alkanic acid's post-conjugation actions. It will also impede glutamic acid's postsynaptic effects by blocking the NMDAR in a non-competitive manner.

In vivo neuropharmacological studies of the anticonvulsant profile of Riluzole lead to the hypothesis that the mechanism of action of this drug may include the blockage of glutamatergic transmission [45]. Several investigations have shown that Riluzole can prevent the effects of exogenous, excitatory amino acids, proving this idea.

Several in vivo and in vitro studies demonstrated that Riluzole decreases excitatory amino acid-evoked neurotransmitter release in a variety of species [46]. Although the results of these studies support glutamic acid antagonism, none of them address the question of whether Riluzole reduces the neuronal response to excitatory amino acids directly and selectively. In vitro research elucidates the mechanism of anti-glutamatergic activity in greater detail and these potential sites of action of an anti-excitotoxic drug are described in Figure 1.



**FIGURE 1.** Potential sites of action of Riluzole

These include: (A) inhibition of glutamic acid release; (B) excitatory amino acid receptor blockade; (C) Voltage-dependent sodium channels are blocked on nerve terminals and cell bodies. (D) Nerve endings and cell bodies are inhibited by voltage-dependent sodium channels; or (E) intracellular calcium buffering mechanisms are activated.

#### ***Advantages of Riluzole***

Many of the gene alterations found in AD are restored by riluzole according to a recent study led by Ana Pereira et al in young and old rats [47]. Riluzole therapy, for example, increased glutamate transporter (EAAT2) expression in the hippocampus, suggesting that effective glutamate removal may avoid excitotoxicity and underpin neuroprotection and better cognitive abilities. Riluzole treatment resulted in an increase of 908 gene transcripts and a decrease of 927 gene transcripts in the animals. Notably, there is a high overlap of genes (435) that were altered by Riluzole medication and those that were altered by aging. Synaptic transmission and plasticity were among the mechanisms disrupted by Riluzole therapy.

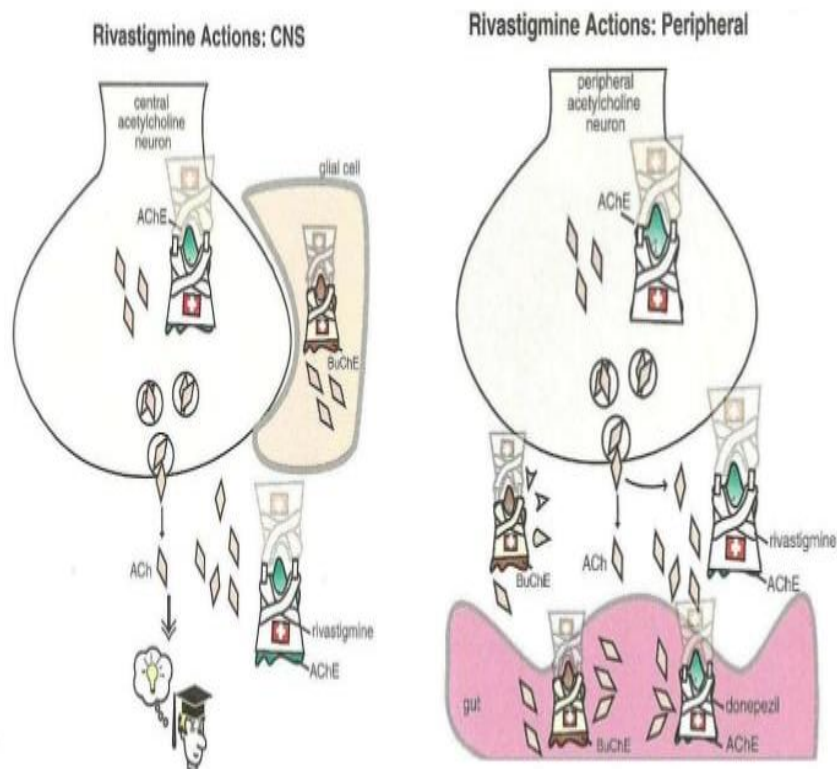
Expression of NMDA glutamate receptor NR2b subunit (GRIN2b), Microtubule-associated protein 1B, enhanced sodium channel subunit (Scn2a1), calcium-calmodulin protein kinase II alpha (CAMK2A) (MAP1B), MAP1B scaffold proteins (MAP1B synaptic scaffold), and protein kinase II beta calcium-calmodulin (CAMK2B), and calcium (MMP9). Riluzole therapy enhanced the expression of several neuroprotective genes

including Tropomyosin B receptor kinase (TrkB; NTRK2), and neurotrophic protein receptor BDNF.

Riluzole is a substrate of P-glycoprotein, a transporter that regulates the removal of numerous substances from the brain, including cholesterol, lipids, peptides, and brain-active drugs [48]. At the blood-brain barrier, it is strongly expressed. P-glycoprotein expression and activity are increased in ALS, resulting in Riluzole, resistance [49]. In both normal aging and Alzheimer's disease, P-glycoprotein expression appears to be decreased suggesting that Riluzole resistance may be less evident; yet, Riluzole is actively pumped out of the brain as long as P-glycoprotein is present [50].

#### ***Rivastigmine: mechanism of action***

Rivastigmine is an AChEI with a unique structural formula compared to other AChEIs on the market today. Rivastigmine attaches to AChE in the same way as ACh does, causing the carbamate moiety to "flatten" over the esteratic site, resulting in prolonged inhibition of AChE. Rivastigmine, like tacrine and donepezil, is hydrolyzed, but unlike these two medications, it leaves the esteratic site carbamylated and the phenolic derivative is swiftly removed [51]. The carbamylated form of AChE is sequestered, preventing ACh from being digested by the enzyme. And its mechanism of action of Rivastigmine was shown in Figure 2.



**FIGURE 3:** Rivastigmine (Mechanism of action)

### ***Combination therapy of AD***

Monotherapy has several disadvantages in treating AD, including safety, efficacy, and disease modification. Moreover, a single drug is unlikely to target a single molecular target that can impact disease development by causing enough changes in AD pathogenesis. Furthermore, single-drug therapy is generally more successful at large dosages, whereas it is more likely to have significant adverse effects at the same doses. This is especially true when it comes to AChEIs. In a dose-dependent manner, their tolerability decreases while their efficacy increases. Treatment with a mix of medicines with diverse mechanisms of action may be more helpful than monotherapy in the context of a successful pharmacological strategy.

### ***Advantages of Rivastigmine plus Riluzole therapy***

Riluzole has beneficial effects such as Hyper-pTau, cognitive decline, excessive glutamate

release, and excitotoxicity, synaptic transmission, (downregulated genes for neurotransmission become upregulated). It affects five pathways and, more crucially, upregulates numerous genes that are downregulated in AD.

Rivastigmine binds to AChE in the same way that ACh does, causing the carbamate moiety to "flatten" over the esteratic site and inhibiting AChE for a long time. Rivastigmine is hydrolyzed in the same way that tacrine and donepezil are, however unlike these two drugs, it leaves the esteratic site carbamylated and the phenolic derivative is quickly eliminated [52]. The carbamylated form of AChE is sequestered, preventing ACh from being digested by the enzyme. The author's comparison table for Clinical trials in Alzheimer's disease using a combination of cholinesterase inhibitors and meantime was given in Table 1.

**TABLE 1:** Clinical trials in Alzheimer's disease using a combination of cholinesterase inhibitors and memantine

Drug combination	No. of volunteer	Disease condition	Time period	Effect	References
ChEIs + memantine	47	Alzheimer's disease (AD)	48 weeks	Between the two study periods, there was no discernible. There is variation in the rates at which total brain volume changes. Treatment with memantine has also been associated with improved executive function and a reduction in right hippocampus atrophy.	[53]
Rivastigmine + memantine	172	Mild to moderate AD	24 weeks	There were no notable differences in ineffectiveness. In terms of safety and tolerability, there were no significant differences between treatment groups.	[54]
Memantine + rivastigmine	176	176 Mild-to-moderate AD	25 weeks	In terms of tolerability, there were no noticeable changes between treatment groups. There are no discernible variations in cognitive or overall performance.	[55]
ChEI + memantine	943	Probable AD	At least a 1-year follow-up	Increasing the time, it takes to be admitted to a nursing home.	[56]
Rivastigmine + memantine	90	Mild-to-moderate and moderate-to-severe AD	12 weeks	As secondary memory matures, attention/executive function improves.	[57]
ChEI + memantine	677	Moderate to severe AD	24 weeks	Significant improvements in the severe impairment battery (SIB), as well as variable impression data based on Clinician Interview Plus (CIBIC+) and safe and well-tolerated treatment.	[58]
ChEI + memantine	433	Mild to moderate AD	24 weeks	No statistically significant differences were found. in the measurement of scores between the memantine and placebo groups.	[59]
Donepezil + memantine	404	Moderate to severe AD	24 weeks	In comparison to monotherapy, combination therapy improved SIB an, CIBIC+ data, in addition to the research activity of advertising cooperation with a daily live list (ADCSADL) decreases.	[60]
ChEI + memantine	382	AD	4 years	When compared to ChEI and no therapy, CT slows cognitive and functional decline.	[61]
Rivastigmine + memantine	202	Moderately severe AD	28 weeks	It's possible that switching to rivastigmine from donepezil or galantamine will improve cognition and behaviour. The addition of memantine could be beneficial.	[62]



## CONCLUSION

Alzheimer's disease (AD) is a long-term neural system disorder that affects patients. Many efforts are currently being made to better understand the pathology of Alzheimer's disease and develop effective treatments. These approaches aim to slow disease progression while also improving patient quality of life. Despite this, there is no effective medication that can halt the progression of the disease. It is difficult to make an accurate diagnosis of Alzheimer's disease. Regional brain atrophy, which is associated with the deterioration of cognitive and functional modifications in Alzheimer's disease, is theoretically linked to the disorder's increasing neuropathological changes.

The role of abnormal amyloid production in the neuropathology of AD has been highlighted in research looking into possible neurotoxic routes. They propose a two-stage genesis of senile amyloid plaques, with secondary development of local acute toxicity, for which higher BChE levels in plaque structure could serve as a marker and potentially dangerous agent.

The various effects of AChEIs, which are routinely used in the hopes of providing symptomatic relief to Alzheimer's patients, could be used as a proof-of-concept to study this theorized neurodegenerative process clinically. Donepezil and galantamine are AChE-specific inhibitors, whereas rivastigmine inhibits both AChE and BChE, which may affect local plaque toxicity. Many potential mechanisms are involved in the origin of neurodegenerative disease and progression, including aerophilic stress, excitotoxicity, mitochondrial pathology, intestinal tissue activation, protein abnormalities, and RNA processing, according to research in the field of neurodegenerative disease. Riluzole appears to be a promising treatment for neurodegenerative disorders. The drug can be formulated in various drug delivery systems for further advancements in the research field. Due to its logical nature, combination therapy is already widely used in clinical practice. Despite the fact that compounds with combined cholinergic–glutamatergic action have been studied, none have yet proven to be successful in later stages of development. As a result,

combination therapy now includes the administration of both a cholinergic inhibitor drug (Rivastigmine) and a glutamatergic antagonist drug (Riluzole). This review demonstrates that Alzheimer's disease combination therapy appears to be safe and well-tolerated for the treatment of moderate to severe AD.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

1. Plamena R. Angelova, Andrey Y. Abramov. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. *FEBS Letters*. 2018; 592(5):692-702. doi:10.1002/1873-3468.12964.
2. Daniel M Skovronsky, Virginia M-Y Lee, John Q Trojanowski. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. *Annu Rev Pathol*. 2006; 1:151-70. DOI: 10.1146/annurev.pathol.1.110304.100113, PMID: 18039111.
3. Paolo Stanzione, Domenicantonio Tropepi. Drugs and clinical trials in neurodegenerative diseases. *Ann Ist Super Sanita* 2011;47(1):49-54. DOI: 10.4415/ANN\_11\_01\_11, PMID: 21430339.
4. Bogousslavsky J, Boller F, Iwata M, editors. *A History of Neuropsychology*. Front Neurol Neurosci. Basel: Karger; 2019.
5. Lipowski Z.J. *Psychosomatic Medicine and Liaison Psychiatry*. Springer: New York, NY; 1984.
6. Jibson Michael, Seyfried Lisa. *DSM-5 Teaching Materials: A Critical Review*. *Academic Psychiatry*. 2016; 41. 10.1007/s40596-016-0614-z.
7. Alzheimer's Association. *Alzheimer's disease Facts and Figures*. *Alzheimer's Dement* 2016 Apr;12(4):459-509. DOI: 10.1016/j.jalz.2016.03.001, PMID: 27570871.
8. Robert H Brown, Ammar Al-Chalabi. *Amyotrophic Lateral Sclerosis*. *N Engl J Med* 2017 Jul 13;377(2):162-172. doi:

- 10.1056/NEJMra1603471, PMID: 28700839.
9. Narwat A, Sharma V, Kumar S, Rani S. Recent advances in pharmacotherapy of alzheimer's disease. *Int j curr pharm res.* 2021;13(6):20-3. Doi: <https://dx.doi.org/10.22159/ijcpr.2021v13i6>.
  10. Domenico Praticò. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci.* 2008 Dec;29(12):609-15. doi: 10.1016/j.tips.2008.09.001, PMID: 18838179.
  11. Swetha G, Anjali R, Saniya Tabassum Dz. Oxidative stress in alzheimer's disease—evaluating the amyloid beta hypothesis. *Int j curr pharm res.* 2021;13(5):32-8. Doi: <https://dx.doi.org/10.22159/ijcpr.2021v13i5>.
  12. Antonio Federico, Elena Cardaioli, Paola Da Pozzo, Patrizia Formichi, Gian Nicola Gallus, Elena Radi. Mitochondria, oxidative stress and neurodegeneration. *J Neurol Sci.* 2012 Nov 15;322(1-2):254-62. doi: 10.1016/j.jns.2012.05.030, PMID: 22669122.
  13. M L Crismon . Tacrine: first drug approved for Alzheimer's disease. *Ann Pharmacother.* 1994 Jun;28(6):744-51. doi: 10.1177/106002809402800612, PMID: 7919566.
  14. Agneta Nordberg , Clive Ballard, Roger Bullock, Taher Darreh-Shori, Monique Somogyi. A review of butyrylcholinesterase as a therapeutic target in the treatment of Alzheimer's disease. *Prim Care Companion CNS Disord.* 2013;15(2):PCC.12r01412. doi: 10.4088/PCC.12r01412, PMID: 23930233.
  15. E L Conway. A review of the randomized controlled trials of tacrine in the treatment of Alzheimer's disease: methodologic considerations. *Clin Neuropharmacol.* 1998 Jan-Feb;21(1):8-17. PMID: 9579280.
  16. N Qizilbash, A Whitehead, J Higgins, G Wilcock, L Schneider, M Farlow. Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. *Dementia Trialists' Collaboration. JAMA.* 1998 Nov 25;280(20):1777-82. doi: 10.1001/jama.280.20.1777, PMID: 9842955.
  17. M Farlow , S I Gracon, L A Hershey, K W Lewis, C H Sadowsky, J Dolan-Ureno. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. *JAMA.* 1992 Nov 11;268(18):2523-9. PMID: 1404819.
  18. Jennifer Y Y Szeto, Simon J G Lewis. Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia. *Curr Neuropharmacol.* 2016;14(4):326-38. doi: 10.2174/1570159x14666151208112754, PMID: 26644155.
  19. Alireza Atri. Current and Future Treatments in Alzheimer's Disease. *Semin Neurol.* 2019 Apr;39(2):227-240. doi: 10.1055/s-0039-1678581, PMID: 30925615.
  20. Joanne Knowles. Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes. *Core Evid.* 2006;1(3):195-219. PMID: 22500154.
  21. Atsushi Tanaka, Shoichi Koga, Yoshihiro Hiramatsu. Donepezil-induced adverse side effects of cardiac rhythm: 2 cases report of atrioventricular block and Torsade de Pointes. *Intern Med.* 2009;48(14):1219-23. doi: 10.2169/internalmedicine.48.2181, PMID: 19602789.
  22. Weinstock, M. Selectivity of Cholinesterase Inhibition. *Mol Diag Ther.* 1999; 12, 307–323 <https://doi.org/10.2165/00023210-199912040-00005>.
  23. Michael Shanks, Miia Kivipelto, Roger Bullock, Roger Lane. Cholinesterase inhibition: is there evidence for disease-modifying effects?. *Curr Med Res Opin.* 2009 Oct;25(10):2439-46. doi: 10.1185/03007990903209332, PMID: 19678754.
  24. Steven Ferris, Agneta Nordberg, Hilka Soinen, Taher Darreh-Shori, Roger Lane. Progression from mild cognitive impairment to Alzheimer's disease: effects of sex, butyrylcholinesterase genotype, and rivastigmine treatment. *Pharmacogenet Genomics.* 2009 Aug;19(8):635-46. doi: 10.1097/FPC.0b013e32832f8c17, PMID: 19617863.
  25. Marwan N Sabbagh, Martin R Farlow, Normal Relkin, Thomas G Beach. Do cholinergic therapies have disease-modifying effects in Alzheimer's disease?. *Alzheimers Dement.* 2006 Apr;2(2):118-25. doi: 10.1016/j.jalz.2006.02.001, PMID: 19595868.
  26. Thibault B Ali, Thomas R Schleret, Brian M Reilly, Winston Yuchen Chen, Ruben Abagyan. Adverse Effects of Cholinesterase Inhibitors in Dementia, According to the Pharmacovigilance Databases of the United-States and Canada. *PLoS One.* 2015 Dec 7;10(12):e0144337. doi: 10.1371/journal.pone.0144337, PMID: 26642212.
  27. Hermann Am Mucke.. The case of galantamine: repurposing and late blooming of a cholinergic drug. *Future Sci OA.* 2015 Sep 3;1(4):FSO73. doi: 10.4155/fso.15.73, PMID: 28031923.
  28. Natalia M Kowal, Philip K Ahring, Vivian W Y Liao, Dinesh C Indurti, Benjamin S Harvey, Susan M O'Connor, Mary Chebib, Elin S Olafsdottir, Thomas Balle. Galantamine is not a positive allosteric modulator of human  $\alpha 4\beta 2$  or  $\alpha 7$  nicotinic acetylcholine receptors. *Br J Pharmacol.* 2018 Jul;175(14):2911-2925. doi: 10.1111/bph.14329, PMID: 29669164.
  29. E N Popova, N N Bogolepov. Changes in neurons of certain regions of the brain under the influence of nivaline. *Bull Exp Biol Med.* 1965;59:572–

- 577.
30. D S Woodruff-Pak, R W Vogel 3rd, G L Wenk. Galantamine: effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning. *Proc Natl Acad Sci U S A*. 2001 Feb 13;98(4):2089-94. doi: 10.1073/pnas.98.4.2089, PMID: 11172080.
  31. Olin JT, Schneider L. Galantamine for Alzheimer's disease. *Cochrane Database of Systematic Reviews*. 2002; 3: CD001747. DOI: 10.1002/14651858.CD001747.
  32. Sean Lilienfeld. CNS Drug Galantamine--a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. *CNS Drug Rev*. 2002 Summer;8(2):159-76. doi: 10.1111/j.1527-3458.2002.tb00221.x, PMID: 12177686.
  33. Sandra I Mota, Ildete L Ferreira, A Cristina Rego. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. *Neuropharmacology*. 2014 Jan;76 Pt A:16-26. doi: 10.1016/j.neuropharm.2013.08.013, PMID: 23973316.
  34. S M Rothman, J W Olney. Glutamate and the pathophysiology of hypoxic--ischemic brain damage. *Ann Neurol*. 1986 Feb;19(2):105-11. doi: 10.1002/ana.410190202, PMID: 2421636.
  35. D W Choi. Glutamate neurotoxicity and diseases of the nervous system. *Neuron*. 1988 Oct;1(8):623-34. doi: 10.1016/0896-6273(88)90162-6, PMID: 2908446.
  36. D W Choi. Excitotoxic cell death. *J Neurobiol*. 1992 Nov;23(9):1261-76. doi: 10.1002/neu.480230915, PMID: 1361523.
  37. Erin J Kodis, Sophie Choi, Eric Swanson, Gonzalo Ferreira, George S Bloom. N-methyl-D-aspartate receptor-mediated calcium influx connects amyloid- $\beta$  oligomers to ectopic neuronal cell cycle reentry in Alzheimer's disease. *Alzheimers Dement*. 2018 Oct;14(10):1302-1312. doi: 10.1016/j.jalz.2018.05.017, PMID: 30293574.
  38. Rui Wang, P Hemachandra Reddy. Role of Glutamate and NMDA Receptors in Alzheimer's Disease. *J Alzheimers Dis*. 2017;57(4):1041-1048. doi: 10.3233/JAD-160763, PMID: 27662322.
  39. Chris Fox, Monica Crugel, Ian Maidment, Bjorn Henrik Auestad, Simon Coulton, Adrian Treloar, Clive Ballard, Malaz Boustani, Cornelius Katona, Gill Livingston. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS One*. 2012;7(5):e35185. doi: 10.1371/journal.pone.0035185, PMID: 22567095.
  40. David Wilkinson, Nick C Fox, Frederik Barkhof, Ravinder Phul, Ole Lemming, Philip Scheltens. Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial. *J Alzheimers Dis*. 2012;29(2):459-69. doi: 10.3233/JAD-2011-111616, PMID: 22269160.
  41. S Bakchine, H Loft. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. *J Alzheimers Dis*. 2007 Jul;11(4):471-9. doi: 10.3233/jad-2007-11409, PMID: 17656827.
  42. Matthew Smith, Jennie Wells, Michael Borrie. Treatment effect size of memantine therapy in Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord*. 2006 Jul-Sep;20(3):133-7. doi: 10.1097/00002093-200607000-00002, PMID: 16917181.
  43. Stuart A Lipton. Pathologically-activated therapeutics for neuroprotection: mechanism of NMDA receptor block by memantine and S-nitrosylation. *Curr Drug Targets*. 2007 May;8(5):621-32. doi: 10.2174/138945007780618472, PMID: 17504105.
  44. Catherine E Creeley, David F Wozniak, Anthony Nardi, Nuri B Farber, John W Olney. Donepezil markedly potentiates memantine neurotoxicity in the adult rat brain. *Neurobiol Aging*. 2008 Feb;29(2):153-67. doi: 10.1016/j.neurobiolaging.2006.10.020, PMID: 17112636.
  45. Alireza Atri, Lynn W Shaughnessy, Joseph J Locascio, John H Growdon. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2008 Jul-Sep;22(3):209-21. doi: 10.1097/WAD.0b013e31816653bc, PMID: 18580597.
  46. G Giaccone, B Pedrotti, A Migheli, L Verga, J Perez, G Racagni, M A Smith, G Perry, L De Gioia, C Selvaggini, M Salmona, J Ghiso, B Frangione, K Islam, O Bugiani, F Tagliavini. A possible link between amyloid and neurofibrillary tangles in Alzheimer's disease. *Am J Pathol*. 1996 Jan;148(1):79-87. PMID: 1861592.
  47. J P Hubert, A Doble. Ibotenic acid stimulates D-[3H]aspartate release from cultured cerebellar granule cells. *Neurosci Lett*. 1989 Jan 30;96(3):345-50. doi: 10.1016/0304-3940(89)90403-5, PMID: 2541382.
  48. L. Barbeito, A. Chérymy, G. Godeheu, J. M. Desce, J. Glowinski. Glutamate Receptors of a Quisqualate-Kainate Subtype are Involved in the Presynaptic Regulation of Dopamine Release in the Cat Caudate Nucleus in vivo. *Eur J Neurosci*. 1990;2(4):304-311. doi: 10.1111/j.1460-9568.1990.tb00422.x, PMID: 12106037.
  49. Anand R, Gharabawi G. Clinical development of Exelon (ENA 713): the ADENA programme. *J*

- Drug Dev Clin Pract 1996;8:9-16. WOS:A1996VJ32200007.
50. Enz A, Floersheim P. Cholinesterase inhibitors: an overview of their mechanism of action. In: Giacobini E, Becker R, editors. Alzheimer's disease. Therapeutic strategies. Boston: Birkhauser, 1994,211–15.
  51. Aline Milane, Christine Fernandez, Sarah Vautier, Gilbert Bensimon, Vincent Meininger, Robert Farinotti. Minocycline and riluzole brain disposition: interactions with p-glycoprotein at the blood-brain barrier. *J Neurochem.* 2007 Oct;103(1):164-73. doi: 10.1111/j.1471-4159.2007.04772.x, PMID: 17635670.
  52. Loqman A Mohamed, Shashirekha Markandaiah, Silvia Bonanno, Piera Pasinelli, Davide Trotti. Blood-Brain Barrier Driven Pharmacoresistance in Amyotrophic Lateral Sclerosis and Challenges for Effective Drug Therapies. *AAPS J.* 2017 Nov;19(6):1600-1614. doi: 10.1208/s12248-017-0120-6, PMID: 28779378.
  53. Md Tanvir Kabir, Md Sahab Uddin, Abdullah Al Mamun, Philippe Jeandet, Lotfi Aleya, Rasha A Mansouri, Ghulam Md Ashraf, Bijo Mathew, May N Bin-Jumah, Mohamed M Abdel-Daim. Combination Drug Therapy for the Management of Alzheimer's Disease. *Int J Mol Sci.* 2020 May 5;21(9):3272. doi: 10.3390/ijms21093272, PMID: 32380758.
  54. Beate Schmitt I, Tanja Bernhardt, Hans-Juergen Moeller, Isabella Heuser, Lutz Frölich. Combination therapy in Alzheimer's disease: a review of current evidence. *CNS Drugs.* 2004;18(13):827-44. doi: 10.2165/00023210-200418130-00001, PMID: 15521788.
  55. Vivian W Chow I, Alena V Savonenko, Tatiana Melnikova, Hyunsu Kim, Donald L Price, Tong Li, Philip C Wong. Modeling an anti-amyloid combination therapy for Alzheimer's disease. *Sci Transl Med.* 2010 Jan 6;2(13):13ra1. doi: 10.1126/scitranslmed.3000337, PMID: 20371462.
  56. Ralf Ihl I, Robertas Bunevicius, Lutz Frölich, Bengt Winblad, Lon S Schneider, Bruno Dubois, Alistair Burns, Florence Thibaut, Siegfried Kasper, Hans-Jürgen Möller, WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force on Dementia. WFSBP Task Force on Treatment Guidelines for Alzheimer's Disease and other Dementias. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of Alzheimer's disease and other dementias. *Int J Psychiatry Clin Pract.* 2015 Mar;19(1):2-7. doi: 10.3109/13651501.2014.961931, PMID: 25195764.
  57. Jeffrey L Cummings. Treatment of Alzheimer's disease: the role of symptomatic agents in an era of disease-modifying therapies. *Rev Neurol Dis.* 2007 Spring;4(2):57-62. PMID: 17609636.
  58. Martin R Farlow, Michael L Miller, Vojislav Pejovic. Treatment options in Alzheimer's disease: maximizing benefit, managing expectations. *Dement Geriatr Cogn Disord.* 2008;25(5):408-22. doi: 10.1159/000122962, PMID: 18391487.
  59. Seong Hye Choi, Kyung Won Park, Duk L Na, Hyun Jeong Han, Eun-Joo Kim, Yong S Shim, Jae-Hong Lee. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. *Curr Med Res Opin.* 2011 Jul;27(7):1375-83. doi: 10.1185/03007995.2011.582484, PMID: 21561398.
  60. Martin R Farlow, Gus Alva, Xiangyi Meng, Jason T Olin. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. *Curr Med Res Opin.* 2010 Feb;26(2):263-9. doi: 10.1185/03007990903434914, PMID: 19929593.
  61. Stuart J Thomas, George T Grossberg. Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clin Interv Aging.* 2009;4:367-77. doi: 10.2147/cia.s6666, PMID: 19851512.
  62. Anton P Porsteinsson I, George T Grossberg, Jacobo Mintzer, Jason T Olin. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res.* 2008 Feb;5(1):83-9. doi: 10.2174/156720508783884576, PMID: 18288936.