



Cholinesterase Inhibitors Used for the Management of Alzheimer's Disease: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Alzheimer's disease (AD) is defined as a progressive neurodegenerative disorder that has lately become the top reason for dementia in the elderly population (usually above 60-65 years). As mentioned before, most AD cases are sporadic and have a late onset. This disease is characterized by impairment of higher cognitive functions like deficits in memory, language comprehension, coordination, etc. The primary pathophysiology behind Alzheimer's disease is loss of cholinergic innervation due to the formation of neuritic (senile) amyloid-beta plaques and tau protein-containing neurofibrillary tangles (NFTs) in parts of the brain associated with memory functions. These neurofibrillary tangles (NFTs) and amyloid β plaques can cause the induction of other aetiologies of Alzheimer's disease-like neuroinflammation and central hyperexcitability. The brain's main regions affected by Alzheimer's disease are the neocortex, the basal nucleus of Meynert, and the hippocampus. These areas are associated with higher cognitive functions like memory, arousal, attention, sensory processing, etc. Thus, cholinesterase inhibitors have been widely used as first-line drug therapy for symptomatic relief in Alzheimer's disease. They function by inhibiting acetylcholinesterase or catabolizing it and henceforth enhancing synaptic availability of

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Acetylcholine. The commonly prescribed drugs of this class include donepezil, galantamine, physostigmine, metrifonate, and rivastigmine. This article will discuss the widely used cholinesterase inhibitors (old & new) for managing AD symptoms in detail.

Keywords: *Alzheimer's disease; a neurodegenerative disorder; sporadic; senile neuritic plaque; dementia; amyloid-beta plaques; tau protein; neurofibrillary tangles; neuroinflammation; central hyperexcitability; neocortex; basal nucleus of Meynert; hippocampus; acetylcholine; cholinesterase inhibitors.*

1. INTRODUCTION

Alzheimer's disease (AD) is defined as a progressive neurodegradative disorder that has recently become the global cause of dementia in the elderly population (above 60 years usually), accounting for 70% of all sporadic, late-onset dementia [1]. This disease is distinguished by progressive deterioration of higher cognitive functions together with a steep decline in the efficiency of daily activities and behavioral changes. AD is the most common type of pre-senile and senile dementia [2].

The brain regions most affected by the characteristic pathology of Alzheimer's disease include the neocortex, hippocampus, basal forebrain, basal nucleus of Meynert, and amygdala. To a lesser extent, the dorsal tegmentum, medial nucleus of the thalamus, locus coeruleus, paramedian reticular area, and lateral hypothalamic nuclei may be affected [3].

Most Alzheimer's disease cases are sporadic, with delayed onset (65 years) and an unknown cause. Age is the most accurate predictor of illness development. However, 5 to 15% of cases are familial; half of these cases have a young (presenile) onset (under 65 years) and are usually linked to specific genetic alterations [1].

2. OBJECTIVE

The following narrative literature review article aims to explore and provide a quick and brief account of AD, its neuropathology, and various medicines belonging to the class of cholinesterase inhibitors used for the symptomatic treatment of Alzheimer's disease in adults.

2.1 Neuropathology of Alzheimer's

The neuropathological manifestations of AD include the deposition of mainly two types of eccentric aggregates of protein- amyloid- β that form neuritic plaques and hyperphosphorylated

tau protein that form neurofibrillary tangles causing massive disintegration of cholinergic neurons in the basal part of the forebrain that leads to loss of neurotransmission of acetylcholine to other areas of the brain, mainly the neocortex via basal nucleus of Meynert and the hippocampus, as these areas are associated with higher cognitive functions like memory, arousal, attention, sensory processing, etc. that are lost in AD [1].

The neurofibrillary tangles of tau protein consist of eccentric aggregations of abnormally phosphorylated tau within the peripheral cytoplasm belonging to certain neurocytes. The poorly structured neurites or neuronal processes in the neuritic senile plaque are surrounded by an inner core and a 4-kD peptide. Other neuropathological lesions may also be seen in Alzheimer's disease, but these two significant lesions define and identify the condition. Other abnormalities include eosinophilic rod-type-looking structures and granular + vacuolar disintegration, which are poorly understood, known as Hirano bodies. . This morphological change, i.e., the loss of the synaptic components, has a clear and marked impact on cognitive functioning [2].

The hallmark mentioned above protein aggregations of Alzheimer's dementia, A β plaques, and neurofibrillary tangles (NFTs) can induce other AD aetiologies like inflammation of neurons and central hyperexcitability. Inflammation of neurons results from the excessive activation of microglial cells and astrocytes that secrete inflammatory chemical mediators like cytokines due to the neural damages caused by A β plaques and NFTs, ultimately contributing to the non-functioning of cholinergic synapses and death of neurons in the basal forebrain [3].

Beta-amyloid protein has been found to have neurotoxic effects. These effects occur through some secondary mechanisms, including lipid peroxidation, oxidation, inflammation, formation

of neurofibrillary tangles, stimulation of apoptotic cell death, and glutamatergic excitotoxicity [4].

Thus, the primary pathophysiology behind Alzheimer's is the loss of cholinergic neurotransmission that manifests in the following ways forming the 'Cholinergic Hypothesis' of Alzheimer':

- Loss of basocortical cholinergic projections.
- Decline in the amount of cortical acetylcholine transferase required for ACh synthesis.
- Destruction of cholinergic neurons in the basalis nucleus or basal nucleus of Meynert [5].

Hence, drugs that can improve cholinergic function and overcome cholinergic insufficiency are essential for managing AD. The widely used drug for symptomatic relief in AD is Cholinesterase Inhibitors.

2.2 Cholinesterase Inhibitors

Most neurotransmitters and neuropeptides, particularly acetylcholine, the critical memory neurotransmitter, fall in concentration inside the human brain as AD progresses. Several ways have improved cerebral acetylcholine levels in Alzheimer's disease. One most effective way is to inhibit the cholinesterase enzyme, making more Acetylcholine available for neurological transmission and leading to cognitive repair [6].

The most effective treatment strategy in dementia associated with Alzheimer's disease is the Cholinesterase inhibitors class. It is seen that the treatment effect is mainly symptomatic in individuals suffering from memory loss (dementia), inhibitors of acetylcholinesterase target the decrease in the concentration of acetylcholine caused by loss of neural cells from projections of the nucleus basalis of Meynert. Hence it is justified that they are symptomatic treatments, with no evidence that they're neuroprotective or change the course of the disease.

They act by inhibiting the catabolic enzyme acetylcholinesterase responsible for hydrolysis and the breakdown of acetylcholine in the synapses. This leads to higher availability of acetylcholine, thereby resolving the cholinergic deficiency of Alzheimer's.

A marked improvement in cognition has been observed when patients are treated with cholinesterases such as galantamine and rivastigmine, and donepezil, which, in a few regions of the brain, decrease acetylcholine, proving the correlation between acetylcholinesterase inhibition and observed cognitive improvement. [7].

Moreover, studies have shown that during the early stages of neuritic senile plaque formation, both butyrylcholinesterase (BuChE) and acetylcholinesterase have an essential role in A β -aggregation. Therefore, by elevating the presence of Ach inside the brain and depleting the A β deposits, the inhibition of AChE and BuChE is a critical target for the successful management and treatment of AD. [8].

Following is a list of drugs which includes both 'not in current use' and 'currently used' cholinesterase inhibitors:

1. Tacrine

In 1993, tacrine became the first licensed medicine used in the management of Alzheimer's. Both AChE & BuChE can be potently inhibited by it. However, tacrine is no longer prescribed because it is poorly tolerated and causes various adverse effects such as dizziness, seizures, diarrhea, syncope, nausea, and vomiting. The GIT side effects were attributable to peripheral cholinergic system overstimulation at or below 30% ChE inhibition, indicating dose-related tolerance. The administration and patient compliance were made difficult because of tacrine's very short half-life and dosing four times a day (QID). In addition, due to hepatotoxic effects, individuals who took medicine had to have their blood checked regularly [9].

Pharmacokinetics: Tacrine is rapidly and thoroughly absorbed following oral treatment. After a single dose of 20-50mg, the peak plasma concentration is attained in thirty minutes to three hours. Tacrine drug has a high distribution, as evidenced by its high volume of distribution. In animal models, organs like the liver, adrenals, kidneys, and brain showed high drug concentrations. Tacrine has a low bioavailability after it is consumed orally, which is assumed to be due to substantial first-pass metabolism. The bioavailability of a drug can be enhanced by administering it rectally. In humans, the

substance is rapidly and extensively metabolized [10].

Adverse effects: diarrhea, seizures, syncope, dizziness, nausea, and vomiting [9].

As mentioned before, Tacrine was found to be hepatotoxic. It was, therefore, discontinued for treatment. Affinity to BuChE was thought to cause the associated liver toxicity [9,11].

2. Physostigmine

Physostigmine was the first AChEI used to study the treatment of Alzheimer's disorder. It is a plant alkaloid isolated from the seeds of Calabar bean, also known as ordeal bean. Its scientific name is 'Physostigma venenosum.' It's a parasympathomimetic capable of crossing the blood-brain barrier (BBB). Its use is less effective due to its limited therapeutic index and short half-life [9]. To address this issue, various types of medication administration have been tested, most recently a controlled-release oral formulation and a transdermal skin patch. It was suggested as a possible treatment for the symptoms of Alzheimer's disease [12].

Pharmacokinetics: To produce systemic effects, physostigmine is injected intravenously or intramuscularly. The half-life is brief due to rapid hydrolysis of the ester bonds by plasma cholinesterase. The kidneys only partially eliminate the active medication. At physiological pH, physostigmine is mainly in the ionized form, even though the non-ionized variant quickly penetrates the BBB and affects the central nervous system. Unlike the quaternary amine cholinesterase inhibitors, which cannot enter the Central nervous system post peripheral injection, quaternary amine cholinesterase inhibitors do [13].

Adverse effects: Physostigmine also has several adverse effects due to which its use has been prohibited; some adverse effects include nausea, vomiting, headaches, diarrhea, and dizziness, to name a few. Earlier, it was prescribed to treat Myasthenia Gravis, glaucoma, and delayed gastric emptying.

However, due to the drawbacks described above, the Physostigmine was not licensed and was soon abandoned for its use in managing Alzheimer's disorder and associated dementia [9].

3. Donepezil

Donepezil is a medication used to manage mild to moderate Alzheimer's disease symptoms. Donepezil is an acetylcholinesterase (AChE) blocker that elevates the amount of accessible ACh. This can help in AD as there's a destruction of functioning cholinergic brain cells, which can be partially compensated by increasing the acetylcholine. Hydrolysis of acetylcholine is prevented as Donepezil is a reversible and specific blocker of acetylcholinesterase (AChE). Donepezil can be used by maintaining steady and high Ach levels, which helps balance the destruction of functioning cholinergic neurons.

It is effective for the three critical components of Alzheimer's disease symptoms: functionality, behavior, and cognition [4].

Pharmacokinetics: Donepezil has a dosage suitable once-daily for its 70-hour half-life. Within three months of treatment, the plasma concentration of donepezil achieves a steady-state and remains stable. In the plasma, long-term donepezil concentrations are dose-proportional, which is consistent with its short-term concentration profile [14].

Adverse effects: It is known that Donepezil has a relatively safe side-effect profile. The most typical adverse effects of donepezil include dizziness, malaise, nausea, insomnia, and diarrhea. Over-excitement, agitation, aggression, irrational dreams, and nightmares have also been rarely associated with the use of Donepezil. Heart disturbances, arrhythmias, and hepatic disorders were not reported using this drug [15].

For severe, moderate, and mild dementia, Donepezil has been approved and is used. It, however, cannot be prescribed for other types of dementia. Even though this drug is not indicated for cognitive impairment, it has been observed to improve these symptoms [9].

4. Rivastigmine

Rivastigmine was first licensed in 2000 for its clinical application. It was used in mild-to-moderate Alzheimer's disease and approved for Parkinson's dementia. It is a carbamate pseudo irreversible inhibitor of Acetylcholinesterase and butyrylcholinesterase, which inhibit ChE-I selectively in the central nervous system. Rivastigmine is highly capable of penetrating the BBB [16,9].

This drug is also available in the form of a skin patch or transdermal patch, making the drug administration easier and increasing patient compliance [17].

Both the esterases and ionic sites of AChE and bound by Rivastigmine, inhibiting its ability to metabolize ACh, but it dissociates considerably more slowly than AChE ("pseudoir-reversible" action). At the synapse, AChE and BuChE metabolize rivastigmine.

Pharmacokinetics: Rivastigmine is rapidly absorbed after 0.8–1.7 hours, and it's best to take it with food to avoid an upset stomach. It has a 35 percent oral to intravenous bioavailability, attaining peak concentration in 1.4–3.8 hours but clearing quickly in 0.3–3 hours. Rivastigmine inhibits both Acetylcholinesterase and butyrylcholinesterase, which depends on the dose of the drug administered, ranging from 20% to 24% at low concentrations (2 mg/d) to a maximum of 62 percent at high concentrations (12 mg/d) [18].

Adverse effects: Adverse effects are mainly cholinomimetic gastrointestinal symptoms. These effects include nausea, vomiting, and diarrhea. It did not prove to show any significant effect on cardiac function. It has been found that Rivastigmine is safe and effective in managing most behavioral, functional, and cognitive abnormalities of Alzheimer's disease [13].

5. Galantamine

Galantamine, which is now artificially synthesized, was derived from many plants, including daffodil bulbs. Galantamine is an acetylcholinesterase inhibitor that is selective, competitive, and reversible. It has been found that this drug also enhances cholinergic nicotinic neurotransmission. This effect is due to its action on the nicotinic cholinergic receptors as an allosteric modulator [19].

Galantamine's therapeutic effect is thought to be primarily related to its nicotinic acetylcholine receptor sensitizing activity rather than overall cholinergic increase due to cholinesterase suppression [9]. Galantamine has a high bioavailability, a comprehensive clearance volume, and low plasma protein binding [20].

In February 2001, this drug was approved to treat Alzheimer's disease (mild-to-moderate) [9].

Pharmacokinetics: The bioavailability of Galantamine is approximately 90%. It also shows a linear pharmacokinetic profile. It has a high distribution volume and a low protein binding rate. The isoenzymes principally responsible for its metabolism are CYP2D6 and CYP3A4, which are the members of the cytochrome p450 family. Clearance of this drug is variable, and the factors which govern it include age, body weight, and sex [21].

Adverse effects: Adverse events seen in galantamine-treated patients usually depend on the dose of the drug administered. These side effects are usually associated with GIT. As the side effects are dose-related, they can be minimized by decreasing the dose of the administered drug [20].

6. Metrifonate

Metrifonate is a drug that was used in the past for the management of schistosomiasis. It is an irreversible, long-acting cholinesterase inhibitor. Its ability to fortify the cholinergic transmission of acetylcholine in the central nervous system led to the development of several clinical trials aimed at improving the treatment of individuals with Alzheimer's disease (AD) [22].

Metrifonate is metabolized and broken down non-enzymatically into a molecular form that forms a stable bond with the catalytic site of acetylcholinesterase (AChE). There is a long-lasting inhibition of both AChE and butyrylcholinesterase. This is why Metrifonate is used once a day for symptomatic relief in Alzheimer's disease patients [23].

Pharmacokinetics: Metrifonate is absorbed rapidly following oral treatment and reaches a peak plasma concentration in about 1–2 hours. It goes through a chemical transition to become dichlorvos, the active compound. Dichlorvos is metabolized quickly and extensively, and it is primarily eliminated in the urine [24].

Adverse effects: When Metrifonate was used for a short term, the side effects of metrifonate were limited and of low risk. However, when used for a longer duration, there were cases of respiratory paralysis and neuromuscular transmission malfunction, which was akin to a myasthenic crisis [9] an infrequent side effect associated with metrifonate was severe bradycardia that could go as low as five beats per minute [23].

It was seen that the beneficial consequences seen in patients treated with Metrifonate ranged from elevated cognition, enhanced behavior, and improved daily function. These effects were present several days and months after Metrifonate administration was initially started [23-31].

3. CONCLUSION

It can be concluded that cholinesterase inhibitors are a class of drugs that prove to be quite effective against symptomatic relief in Alzheimer's disease. However, out of all the Acetylcholinesterase inhibitors discussed above, Tacrine and Physostigmine are the ones that are not in use anymore because of their several undesirable adverse effects.

However, with new research, there has been the development of new drugs, the latest being Aducanumab that directly acts at the root pathology of Alzheimer's disease and helps actually to treat the illness.

More extensive research for the treatment of Alzheimer's associated dementia is necessary and indeed is the need of the hour.

DISCLAIMER

The products used for this research are commonly and predominantly used in our research area and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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