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ALZHEIMER'S DISEASE AND ITS EFFECTIVE PHARMACOLOGICAL MANAGEMENT

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ABSTRACT

Dementia caused by Alzheimer's disease (AD) is characterized by a specific neuropathology and onset and progression of cognitive and functional impairment that is age-related. Alois Alzheimer initially discussed the patient he first saw in 1901 in his description of him in 1906. Neurodegenerative disorders are brought on by intracellular Amyloid plaques, neurofibrillary tangles, and extracellular amyloid protein depositions. Generally three hypotheses were proposed such as Tau hypotheses, Cholinergic hypothesis and Amyloid hypothesis which makes Alzheimer's an multifactorial diseases. The condition is also influenced by a number of risk factors, including increased age, infections, brain trauma, and vascular disease. However, to combat it, several medications have been approved, such as cholinesterase enzyme inhibitors and N-methyl D-aspartate (NMDA) antagonists, which have a major influence on treating symptoms but are unable to treat AD.

KEYWORDS: Alzheimer's Diseases, Tau Hypothesis, Neurofibrillary tangles, Acetylcholinesterase, Galantamine, Memantine.

INTRODUCTION

According to the WHO, Alzheimer's disease is the primary cause of dementia, accounting for 60% to 80% of all cases.[1,2,3] T Dementia is the most prevalent cause of dependency and disability in the world. Memory, thinking, cognition, and eventually daily living skills are all affected by Alzheimer's disease, a psychiatric disorder that deteriorates with age.[1] It is a CNS disorder that predominantly affects the entorhinal cortex, temporal lobe and

hippocampus before progressing to the cerebral cortex, which may be in responsibility of social behavior, reasoning, language and ultimately causing death. When illness worsens, brain develops Lewy bodies, neurofibrillary tangles, and amyloid plaques.[1,4]

Family members and the patient may notice the symptoms even if the problem may appear to be minor. The current standard for determining if someone has Alzheimer's is cognitive impairments that are severe enough to interfere with everyday functioning (MCI- Mild Cognitive Impairment).[5] Cognitive and functional abilities, particularly visuospatial and executive function, gradually diminish with Alzheimer's disease. Increased dependency and neurological deterioration (akinetic mutism) are signs of the condition's final stages.[6]

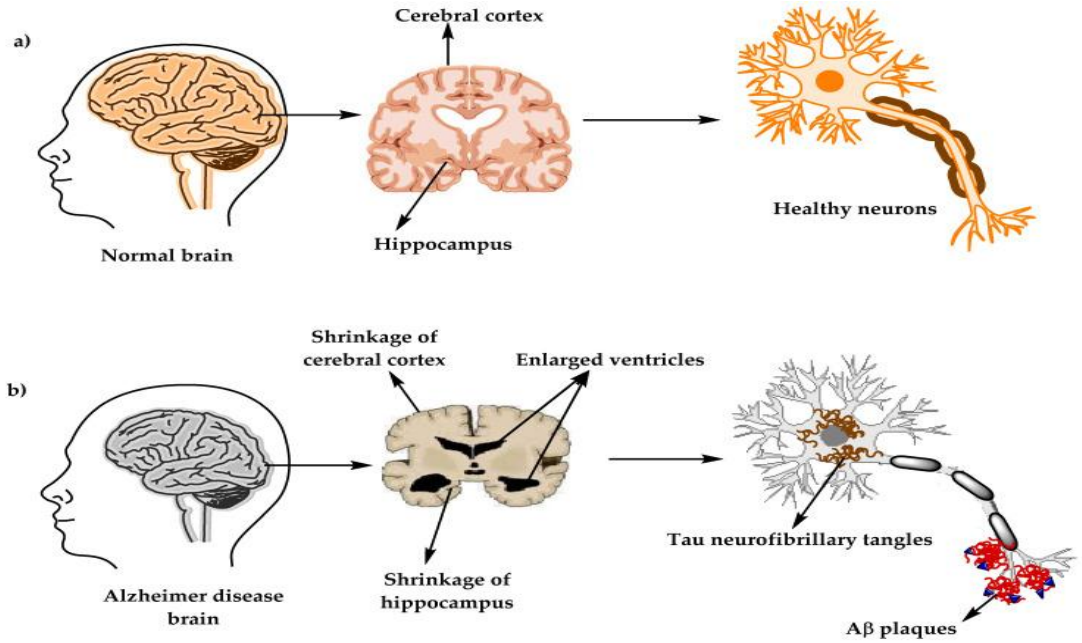


Figure 1: https://doi.org/10.3390%2Fmolecules25245789.

Neuroimaging is utilized to look for other diseases that may produce symptoms similar to Alzheimer's since clinical findings from the patient are used to diagnose Alzheimer's disease. Future Alzheimer's diagnostic criteria will probably include laboratory tests such molecular/functional neuroimaging, genetic testing, and biomarker analysis to increase sensitivity, especially throughout the disease's early and late phases. There is currently no ideal treatment for Alzheimer's disease because the disease's causes are not well understood. With medication and therapy, the condition can only be delayed from progressing. There are several medicinal treatments for Alzheimer's disease, including acetylcholinesterase inhibitors, antioxidants, NMDA channel blockers, and others. Critical aspects of treatment

include how the disease is managed and how medications affect the brain. Many aspects of the neuropharmacology of AD are examined in literature that is now available.[7,8]

History of alzheimer's

Alzheimer's disease is named after German pathologist and psychiatrist Dr. Alois Alzheimer in 1906. A woman who had died from a rare mental condition showed changes in her brain tissue, according to him. She displayed unusual behaviour, speaking difficulties, and memory loss. He examined her brain as she died and discovered numerous aberrant clusters (such as amyloid plaques) and tangled fibre bundles (such as tau tangles).[5] Eleven further instances of the same illness were reported only as Alzheimer's disease in five years. When referring to Alzheimer's in adults 65 and older, at first, the condition was known as "senile dementia of the Alzheimer's type" (SDAT). On the other hand, persons who were younger are thought to have the classic form of the condition.[9]

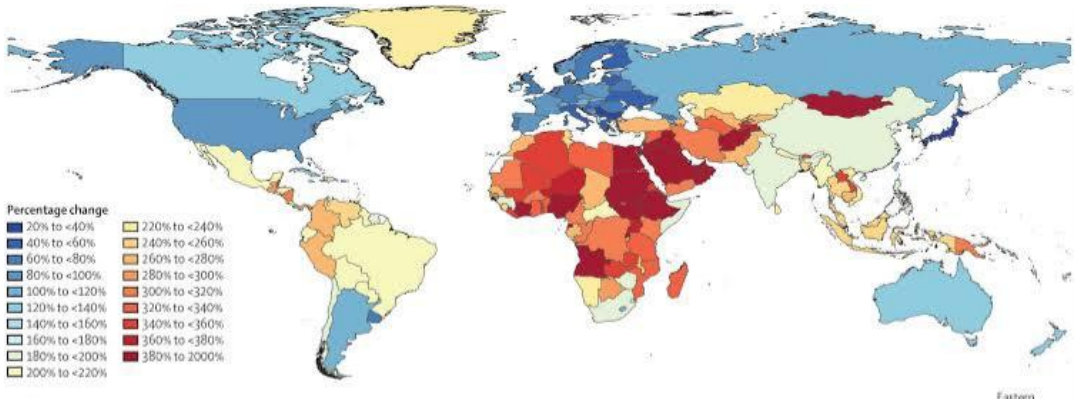
In comparison to countries with greater medium incomes (138%), lower middle incomes (185%), and low income countries (239%, a nearly threefold increase), higher income countries are predicted to see only between 2015 and 2050, there will be a 56% increase in the number of senior citizens residing there. Globally, 46.8 million people were expected to have dementia in 2015. Between 2030 and 2050, its population will nearly double every 20 years, reaching 74.7 million. Comparing the most recent figures to those from the 2009 Global Alzheimer Report, there is a 12–13% increase. According to our projections, there will be 9.9 million new instances of dementia per year. Or one case every five minutes and 3.2 seconds, predicated on a meta-analysis of the data available. Dementia incidence rates doubles every 6.3 years as people get older, age 60–64: 3.9 per 1000 person-years; age 90+: 104.8 per 1000 person-years; according to all studies that have been combined.[10,11]

Figure 2: http://dx.doi.org/10.31782/IJCRR.2022.14205.

Alzheimer's disease progression results in the brain's degeneration by killing brain cells. The brain shrinks more and more as the condition becomes worse as shown in figure.

Epidemiology of alzheimer's

In epidemiological investigations, prevalence and incidence are the two primary metrics. The number of new instances per unit of person-time at risk is known as the incidence. Prevalence is the term used to describe the overall number of illness cases that are present in the community at any one period. Alzheimer's disease causes 50% of all new cases of dementia each year.[12] Above the age of 65, the risk of acquiring the illness nearly doubles every five years, going from 3 to 69 per thousand person years. The disease's incidence rates differ depending on age, which is a primary risk factor. The longer lifespan of women may be the reason why they are more prone than men to get Alzheimer's disease. Estimates show that the frequency of Alzheimer's dementia was 5.3% in those between the ages of 60 and 74, 13.8% in those between the ages of 74 and 84, and 34.6% in those beyond the age of 85.[13,14]



By 2050, there would be 1528 million cases of dementia worldwide, up from 574 million cases in 2019 (95% confidence interval: 504-651). Age-standardized both-sex prevalence remained steady between 2019 and 2050 (global percentage change of 1% [-75% to 108%]), despite considerable expected increases in the number of dementia sufferers. We predicted that there would be more women than males suffering from dementia in 2019.[15,16]

Pathophysiology of alzheimer's

The loss of neurons and synapses in parts of the cerebral cortex and subcortical regions characterizes Alzheimer's disease. Gross atrophy results from this loss in the afflicted regions, including degeneration in the parietal and temporal lobes and sections of the frontal cortex (17). Alzheimer's disease brains and the hippocampus have neurofibrillary tangles and

A plaques that are readily visible under a microscope.[18,19] Beta-amyloid peptide and cellular debris accumulate in thick deposits called plaques outside and around neurons. The hyperphosphorylated aggregates of tau, a protein related with microtubules, build up inside of cells and are known as tangles (neurofibrillary tangles). Even though many older people experience plaques and tangles as they age, those who have Alzheimer's disease have more of them in particular parts of the brain, such the temporal lobe.[20]

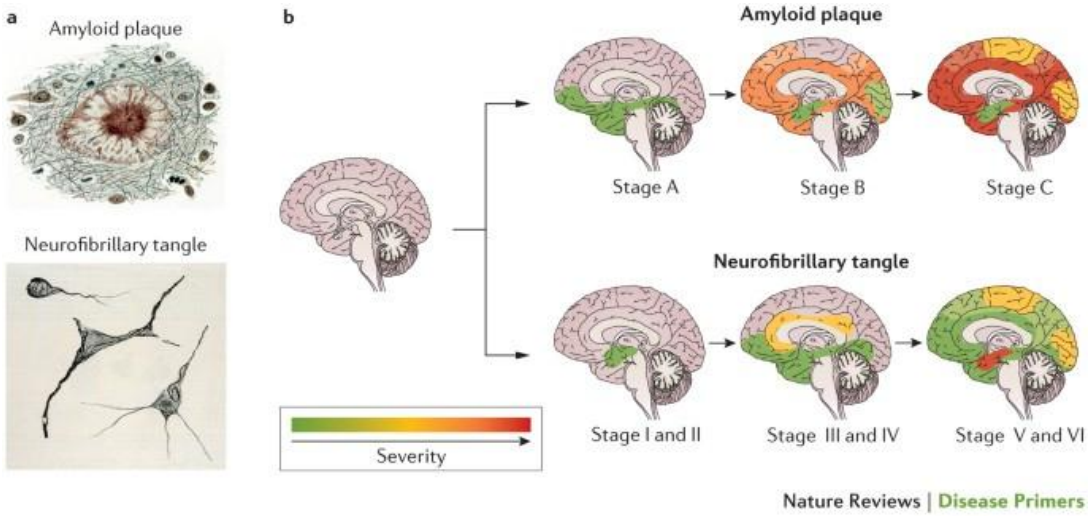


Figure 3: https://doi.org/10.1038/nrdp.2015.56.

Mechanism of diseases

According to the amyloid hypothesis, beta-amyloid peptide accumulation is the main factor contributing to neuronal degeneration. The buildup of aggregated amyloid fibrils, which are thought to be the toxic form of the protein that upsets the calcium ion balance in the cell, results in programmed cell death (apoptosis).[21] The pathogenesis of Alzheimer's disease may also be influenced by various inflammatory processes including cytokines. Inflammation is a common symptom of tissue damage in all disorders, and in Alzheimer's disease, it could be caused by or be an indication of an immune response.[22] Alzheimer's disease has been associated with modifications in the distribution and expression of many neurotrophic factors, including brain-derived neurotrophic factor (BDNF).[23-25]

Hypothesis related to alzheimer's

In 1976, American neurologist Robert Katzman proposed eliminating the age cutoff separating pre-senile dementia from senile dementia of the Alzheimer's kind. AD was widely accepted as the most prevalent cause of dementia in older persons around the beginning of the 1980s.

There were 3 Hypothesis observed

1) Tau hypothesis
2) Cholinergic hypothesis
3) Amyloid hypothesis

Tau hypothesis

According to neuropathology, intraneuronal neurofibrillary tangles containing tau protein are a hallmark of Alzheimer's disease.[26] Tau proteins, which belong to the family of microtubule associated proteins, are present in the majority of neurons.[27] The tau hypothesis claims that adult-type tau is converted into PHF-tau (paired helical filament) and NFTs by abnormal or excessive tau phosphorylation.[28] The tau protein family consists of six isoforms with an amino acid range of 352-441. Each of the six tau isoforms may have a different physiological function and diverse biological activities because of their differential expression during development and varying effectiveness in stimulating microtubule assembly.[29,30] Tau's capacity to bind microtubules is likely to have both favourable and unfavourable effects. Tau has a beneficial effect by preserving microtubules, enabling neurites to grow and become stable. The drawback is that tau might out-compete kinesin, a motor protein, for microtubule binding, resulting in reduced axonal transit.[31]

Cholinergic hypothesis

A deficiency in central cholinergic neurotransmission is among the most pervasive and significant changes connected to AD, however other neurotransmitter systems may also be altered.[32] The degree of cognitive impairment was correlated with the decline in ChAT activity in AD brains. To stimulate the central cholinergic system and minimise cognitive decline in AD, early clinical investigations using cholinesterase (ChE) inhibitors were conducted. In the synaptic clefts, ChE converts released ACh to choline and acetate. ChE antagonists prevent ACh from being hydrolyzed, which in turn activates cholinergic transmission.[34,35] The cholinergic deficit was discovered in the hippocampus, temporal cortex, prefrontal, and parietal cortex—regions of the brain that are thought to be most severely damaged by AD. The severity of the cholinergic impairment was found to be correlated with the number of senile plaques in the patients' brains and the dementia scores they had gotten on specific scales prior to death.[36] The activity of choline acetyltransferase, a reliable indicator of cholinergic neurons and synapses, was demonstrated to be noticeably diminished, sometimes in a very severe manner, in pathological samples taken from

Alzheimer's patients' brain and hippocampus.[37] It was found that postmortem brain tissue from Alzheimer's patients had decreased activity of the pyruvate dehydrogenase complex, an essential enzyme for the manufacture of acetylcholine. The nucleus basalis of Meynert's cholinergic neurons are where this enzyme is most active.[38] In samples from MCI and early Alzheimer's disease patients, basal forebrain cholinergic neurons that can be identified using immunohistochemistry for choline acetyltransferase or the vesicular acetylcholine transporter were not reduced in comparison to controls.[39]

Amyloid hypothesis

The amyloid hypothesis, also known as the amyloid cascade hypothesis and the A hypothesis, has been the main explanation defining the neurophysiology of Alzheimer's disease for more than 20 years.[40] The most well-known physical signs of the disease are senile plaques, which are predominantly made up of various lengths of beta-amyloid peptides (A). However, plaques themselves are not regarded to be the cause of the illness. Although fibrils and monomers are often non-toxic, it is known that oligomers mediate A's cytotoxicity. These oligomers need to be targeted to stop blocking the synthesis of (Aβ)- and –secretase.[41] The amyloid protein (Aβ) is thought to be the root cause of Alzheimer's disease and to be directly responsible for neurofibrillary tangles, cell death, and dementia according to in-vitro and in-vivo investigations.[42] Growing evidence points to Aβ as a trigger in the early stages of the disease process, despite the fact that the majority of information still supports Aβ as the primary initiator of the complex pathogenic cascade in AD.[43]

Signs & Symptoms

Alzheimer's disease develops indications and symptoms over time. Anyone whose symptoms worsen quickly must visit a doctor for treatment of AD. The elements that are causing the symptoms to worsen can be addressed. The early stage, middle stage, and late stage are generally used to categorize AD symptoms.

Early stage

Memory loss is one of the initial symptoms of Alzheimer's disease (AD), according to patients and caregivers.[44] Patients usually attempt to avoid unpleasant circumstances and minimize or dissimulate their problems. In addition to more complex jobs, the patient's diminished ability to plan, judge, and organize may also be evident in more difficult home tasks (keeping a bank account, making meals, etc).[45] The visual sensory memory seems to be unaffected in the early stages of AD.[46] Simple hearing tests, such as distinguishing, may

reveal deficiencies early in the condition.[47] Olfactory functioning may be impaired in AD early symptoms. Odour discrimination[49,50] and odour recognition and identification[48] also seem to be impacted. Exhibiting depressive symptoms.[45]

Middle stage

The parts of the brain that regulate language, logic, sensory processing, and conscious thought are harmed in the middle stage of Alzheimer's disease. This phase frequently lasts the longest and for the longest durations. Memory loss, confusion, and difficulty identifying relatives and friends all get worse at this stage.[51] When issues worsen when performing regular everyday activities like taking a shower, they can be very annoying and frustrating[52] MCI is frequently accompanied by anterograde memory loss, but some patients also show declines in their linguistic, visuospatial, and executive functions.[53]

Late stage

Amyloid builds up in the form of intracellular and extracellular neurofibrillary tangles in Alzheimer's disease (AD), a neurodegenerative condition. AD worsens over time.[54] Dementia patients who exhibit symptomatic depression may nonetheless be regarded as syndromically depressed even if the illness only sometimes or labilely appears. Even though a dementia patient continuously exhibits their abnormal mood, they may still be disabled if they are unable to support any meaningful cognitive function.[55] Neuropsychiatric symptoms (NPSs) may manifest before dementia. In persons with adequate cognitive function, signs of depression, anxiety, irritability, and apathy suggest a quicker rate of cognitive decline[56] The three stages of NPSs are typically characterized by[56] irritability, depression, and changes in nighttime behaviour[57] anxiety, appetite changes, agitation, and apathy; and[58] elation, motor disturbances, hallucinations, delusions, and disinhibition.[57] At this point, the brain has significantly shrunk, and the cells within the brain have suffered significant damage. At this point, people may not be able to recognize their family or their surroundings, and they may find it difficult to control their movements and physical acts.[57]

Neurotransmitters acting on alzheimer's

Acetylcholine

ACh-producing neurons and other cholinergic neurons play a major role in the pathophysiology of AD. The first neurotransmitter, ACh, was discovered in 1920.[59] The neurotransmitter ACh is produced by cholinergic neurons and subsequently released into the synaptic cleft where it interacts with nAChRs and muscarinic ACh receptors (mAChRs). Ach

directly binds to nAChR, greatly boosting tau phosphorylation as a consequence. Nevertheless, mAChR activation may prevent tau phosphorylation.[60]

Serotonin

Monoamine neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been demonstrated to be vital for modulating motor activity, autonomic reactions, and cognitive behaviour in the central nervous system.[61] Serotonergic neuron loss and hypofunction of the 5-HT neurotransmitter have a role in the behavioral characteristics of AD development.[62] It was shown that the 5-HT levels in the hippocampus of diseased brains had drastically dropped.[63] Based on the transducer mechanisms, the seven categories of 5-HT receptors—numbered 5-HT1 to 5-HT7—have been split.[64] The pathophysiology of AD has been connected to one of these subtypes, 5-HT6 receptors, which are serotonergic learning and memory receptors.[65] This is supported by the discovery that a susceptibility factor in the etiology of AD is the single nucleotide polymorphism C267T in the 5-HT6 receptor gene.[66]

Dopamine

There is evidence that dopamine levels below a micromolar can significantly inhibit the production of amyloid fibrils. Since the D1 receptor appears to be more important for cognitive function, particularly spatial learning and memory processing, D1 agonists are being investigated to improve cognition in AD.[1]

Treatment on alzheimer's

Alzheimer's disease is now incurable. As a result, symptom reduction rather than improving the target molecules is the aim of AD therapy techniques. Although they can be postponed, the consequences and symptoms cannot entirely be undone. In order to treat Alzheimer's disease, The first step is the use of cholinesterase antagonists like Rivastigmine and Galantamine. Second, an NDMA medication called Memantine is used throughout therapy. The general preference is for combination treatment to maximise effectiveness and provide alleviation.

1) Galantamine

Galantamine is a competitive, reversible tertiary alkaloid inhibitor of acetylcholinesterase.[68] AChE is inhibited by the new AD medication galantamine[69] and modulates nicotinic Ach receptors (nAChRs).[70] The medication improves patients' cognition, function, and everyday activities while treating the symptoms of Alzheimer's disease and other kinds of dementia.[71]

Galantamine functions as a reversible, competitive AChE inhibitor, raising synaptic ACh levels. It might also alter the activity of presynaptic nicotinic receptors.[72] In human plasma and erythrocytes, galantamine selectively inhibited AChE rather than butyrylcholinesterase. Along with suppressing AChE, galantamine also interacts directly with nicotinic acetylcholine receptors (nAChRs) and enhances their functionality. The major pathway for galantamine metabolism uses the liver's cytochrome (CYP) P450 isoenzymes, which can metabolize 75% of a dosage of galantamine. Throughout the first 24 hours after intravenous or oral administration, 18 to 22% of the dosage is unchanged removed in the urine. Patients receiving galantamine demonstrated notable improvements in their cognitive function, behavioural symptoms, and daily living skills.[71] Galantamine improved the individuals' performance in instrumental and fundamental daily activities and also slowed the evolution of the behavioural signs linked to the illness process.[73]

2) Rivastigmine: A reversible cholinesterase inhibitor

The pseudo-irreversible carbamate inhibitor rivastigmine tartrate inhibits both AChE and BuChE with a preference for the brain as opposed to peripheral tissue.[74] Rivastigmine primarily inhibits AChE metabolism in the Brain in a reversible manner.[75] On the inhibition of AChE, it likewise shows dose-dependent effects. It binds to AChE's esteratic and ionic sites, inhibiting its ability to metabolise ach.[76] In healthy adults, rivastigmine is rapidly and completely absorbed following oral administration, with a time to maximum concentration (Tmax) ranging from 0.8 to 1.67 h and an absolute bioavailability of about 36%.[77] In the synapses, the target enzymes AChE and BuChE metabolise rivastigmine. Rivastigmine is created when esterases hydrolyze AChE and BuChE, breaking the covalent bonds. Less than 1% of the drug is found in the stool 24 hours after delivery, and more than 90% of it is removed completely by the kidneys.[76] Due to rivastigmine's poor protein binding, the hepatic microsomal cytochrome P450 system does not appreciably metabolise it, hence no clinically relevant drug interactions are anticipated.[74]

3) Memantine

Long-term potentiation is a crucial learning and memory mechanism (LTP). The neurotransmitter glutamate uses the NMDA receptor to mediate LTP. The NMDA receptors are widely distributed throughout the brain. They do, however, heavily fill the dendrites of pyramidal cells in the cortex and hippocampus (areas known to be involved in cognition, learning, and memory).[78] The glutamate that neurons emit is either digested or taken up by

nearby cells under physiological circumstances. The NMDA receptor is overexcited by the accumulating glutamate when these pathways are damaged, which results in pathology that is typical of neurodegenerative illnesses. When glutamate, glycine, or NMDA bind to NMDA receptors, a calcium [II] ion (Ca2+) channel opens.[79] As measured by NNT and effect sizes, the findings of significant clinical trials contrast favourably with those obtained from research utilising AChEIs in mild-to-moderate AD. Memantine has a low frequency of adverse events (AEs), is well tolerated, and exhibits few drug-drug interactions.[80] Based on completion rates, vital signs, an ECG, laboratory data, adverse events (AEs), and serious adverse events (SAEs), memantine at a dose of 10 mg twice daily was safe and well tolerated.[81]

Comparative study of drugs on alzheimer's

Name of Drug	Type of Inhibition/ MOA	Effective Dose (Minimal)	Duration of Action	Side Effects
Galantamine	Acetylcholinesterase & butylcholinesterase Inhibitor	4mg Twice a Day	8 hours	Abdominal Pain, Nausea, Hepatotoxicity
Rivastigmine	Acetylcholinesterase Inhibitor & CNS Selective	1.5mg Twice Daily	7 to 8 hours	Nausea, Vomiting Diarrhea
Memantine	NMDA Receptor Antagonist	5mg Daily	6 to 8 hours	Vomiting, Convulsions Blurred vision

Galantamine has a low protein binding and is metabolized by the liver via CYP2D6, Memantine has a high protein binding and is processed by the liver without the help of CYP, and Rivastigmine has a protein binding of 40% and is metabolized in the brain.

Galantamine and Rivastigmine are typically administered for people in the age range of 40 to 60 who have mild or moderate AD, while memantine is prescribed for patients with severe AD. Cholinergic neurotransmission is inhibited by reversible cholinesterase antagonists, which act as catalysts in the synaptic cleft for the conversion of acetylcholine to choline and acetate varying degrees of AD. Galantamine is a centrally and peripherally acting acetylcholinesterase inhibitor that increases cholinergic tone by inhibiting acetylcholinesterase in the muscles and brain. Memantine and other N-methyl-D-aspartate receptor antagonists are non-competitive medications. It binds to the channel's Mg2+ binding site and restricts activation without doing any damage. It is also used to treat conditions like

Alzheimer's and other neurodegenerative diseases. As studied Memantine use significantly slows clinical deterioration.

CONCLUSION

A study reveals that Alzheimer's disease is a neurodegenerative condition. It can also be hereditary; it also includes extracellular amyloid plaques, intracellular neurofibrillary tangles, and synaptic degradation with neuronal death. It can also be caused by a deficiency of vitamin D or a decrease in the metabolism of glucose in the brain. The current available medications only target the symptoms, not the actual cause. Neurotransmitters play a vital role in the action of drugs for treatment of Alzheimer's. As studied in this review, it is observed that mainly memantine and rivastigmine are used as primary medications in the sub-acute and chronic stages, and it is also affected by the age factor; patients over 65 are kept under observation after administration of these drugs (in special cases only), and for the acute type of Alzheimer's, galantamine and rivastigmine are used.

DISCUSSION

Alzheimer's disease is the most common form of dementia and has a multifactorial etiology, and the current drugs used for treatment do not fully contribute to the well-being of the patients. This is reflected in the recent research program, which found that current available drugs are only effective in symptom treatment without actually treating the cause. The research papers from 1992 till date suggest the development of new drugs that have different targets (neurotransmitters or locations) for the treatment of Alzheimer's.

The current available drugs have effective actions, some therapeutic potential, and a few side effects too. So it is required for the development of new drugs and therapies like AChEIs to be introduced for the more effective and sustainable treatment of AD.

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