Review Article
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Pharmacological management of Alzheimer's disease: a current view

Abstract

Alzheimer's disease is a chronic, multifactorial, and irreversible condition characterized by atrophy beginning in the entorhinal cortex and hippocampus, followed by the cerebral cortex. Clinically, the patient experiences a gradual cognitive decline, losing language, reasoning, and social behavior skills. Treatment involves acetylcholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine) or NMDA receptor antagonists (Memantine). The study described the pharmacodynamic and pharmacokinetic aspects of the main drugs, analyzing absorption, distribution, metabolism, excretion, adverse reactions, and drug interactions from articles in the BVS, Scielo, and Pubmed databases. Pharmacokinetic results show that Memantine is absorbed in 9-12 hours, with a half-life of 60-80 hours; Rivastigmine has rapid absorption, crossing the blood-brain barrier; Galantamine is absorbed from the gastrointestinal tract and metabolized in the liver. Donepezil has high bioavailability, a 70-hour half-life, and is metabolized in the liver. All are excreted by the kidneys. Regarding drug interactions, Donepezil increases the risk of seizures when combined with Tramadol or Bupropion; Galantamine is inhibited by drugs like Ketoconazole, increasing side effects; Memantine interacts with Acetazolamide and other drugs, increasing the risk of neuropsychiatric effects; Rivastigmine can cause bradycardia when combined with beta-blockers and enhances the effects of muscle relaxants. Adverse reactions include dizziness and diarrhea (Memantine), nausea (Rivastigmine), bradycardia (Galantamine), and weight loss (Donepezil). In conclusion, Alzheimer's treatment, while not curative, improves the patient's quality of life and slows the decline in social and cognitive abilities.

Keywords: rivastigmine, donepezil, galantamine, memantine, Alzheimer's disease.

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Introduction

Regarding the definition of AD, it was discovered in 1906 and described in 1907. The name Alzheimer's disease was given by Emil Kraepelin in honor of the professor and clinical psychiatrist Alois Alzheimer (1864-1915), his colleague and student, who after the death of a patient observed the brain under a microscope and noticed the presence of neuritic plaques, neurofibrillary tangles and amyloid angiopathy, characteristic of Alzheimer's disease. These plaques and tangles atrophy some parts of the brain, starting in the entorhinal cortex and hippocampus and later in areas of the cerebral cortex linked to language, reasoning and social behavior, and can reach and damage other areas of the brain.[1,2,4] Responsible for approximately 70% of dementia cases worldwide, AD is a chronic, multifactorial, irreversible brain disease, clinically characterized as a cognitive deficit that gradually worsens, reducing the ability of individuals to perform daily activities. AD is the most common cause of dementia among the elderly, but its symptoms, although rare, can be early and appear from 30 years of age. Neuropsychiatric symptoms are important clinical markers of progression and not only risk factors; they are frequently observed in patients with dementia. Furthermore, a narrative review concluded that some metabolites produced by the intestinal microbiota may be involved in the pathogenesis of AD, considering that the composition of the intestinal microbiota influences the central nervous system. Another retrospective study analyzed patients with heart disease and depression and revealed that these are more likely to have AD.[3,5]

Regarding the epidemiology of AD, the global estimate of the number of individuals affected by dementia, including Alzheimer's, is projected to reach 152 million by mid-century, with particularly significant growth expected in low- and middle-income nations.[6] Projections indicate that the number of Alzheimer's disease (AD) patients aged 65 and older could increase substantially, from 5.8 million to 13.8 million by 2050 in the Americas alone.[7] Community studies in Japan and China over the past few decades have shown an increasing prevalence of AD.[8]

A higher overall age-specific prevalence was observed in women than in men, with a higher age-standardized mortality rate among women, suggesting that factors other than longevity contribute to this gender disparity.[9] The number of deaths attributed to AD increased by 146.2% between 2000 and 2018, making AD the fifth leading cause of death among older Americans. Caregivers of patients with AD face considerable mental stress and negative emotional impacts, creating a significant and challenging social and familial burden.[10]

The presence of pre-existing diseases is more common in patients with AD than in their peers, highlighting the importance of maintaining physical health in preserving cognitive function. Several risk factors are associated with the development of AD, some of which may also manifest as symptoms of the disease, complicating accurate identification. Future challenges include the identification of more sensitive biomarkers and less invasive screening methods to facilitate early diagnosis and the implementation of evidence-based preventive strategies.[11] The prevalence of dementia, especially

clinically diagnosed AD, tends to increase with population aging.[12] Furthermore, studies show that the prevalence of clinically diagnosed AD is associated with increasing age.[13] There is no specific test or biological marker for the diagnosis of Alzheimer's disease. To confirm AD, a combination of medical history, cognitive and functional assessments, neurological tests and blood tests are used to rule out other conditions that may present symptoms similar to Alzheimer's.[14]

Acetylcholinesterase inhibitors (Donepezil, Galantamine and Rivastigmine) are used to treat AD in order to prolong the half-life of acetylcholine in the synaptic cleft, helping with cognitive and motor functions in mild and moderate patients. In addition, memantine can be used as monotherapy or in combination with acetylcholinesterase inhibitors in severe cases, due to the loss of glutaminergic neurons caused by AD. Finally, physical exercise helps to reduce cognitive and functional damage.[15,16] The general objective of this work is to discuss the pharmacodynamics and pharmacokinetic aspects of drugs used in the treatment of Alzheimer's disease (AD). More specifically, to detail the Acetyl cholinesterase Inhibitors and Glutamate Inhibitors, the main drugs used in the treatment of AD. In addition, we seek to review the main drug interactions of the drugs involved in the treatment of AD, analyze the main ADRs (adverse drug reactions) and relate the efficacy of these drugs to their distribution, absorption and metabolism.

Pharmacological treatment

Donepezil

Donepezil, or E2020, is a reversible second-generation acetylcholinesterase inhibitor used in AD to help with the cognitive, functional, and behavioral symptoms of the disease. Studies on the efficacy of AChE-Is began in 1970. The first approval was granted to Tacrine, and soon after to Donepezil, which was approved in November 1996 by the FDA (Food and Drug Administration) and in October 2000 by the Brazilian National Health Surveillance Agency (ANVISA). Donepezil was shown to be 10 times more potent than the acetylcholinesterase inhibition done by Tacrine. Among its advantages, when compared to Tacrine, it is shown to be more tolerable due to fewer side effects and a more convenient dosage. The main effects studied are abdominal pain, nausea, vomiting, diarrhea, anorexia, weight loss, headache, dizziness, fatigue, and drowsiness. The main dosages studied are 5 mg/day of Donepezil for 12 weeks and 5 to 10 mg/day, both showing cognitive improvement and improvement in the performance of ADL and ADL in patients with AD. However, despite its positive points, the biggest disadvantage is associated with the half-life of 73 hours.[17-19]

The molecular formula of donepezil hydrochloride, also called 2-[(1-Benzil-4-pipe ridinil)metil]-5,6 -dimetoxi-1-indano pela IUPAC, is $C_{24}H_{29}NO_3$, shown in Figure I, and average mass of 389.492 Da.[20] (Figure 1).

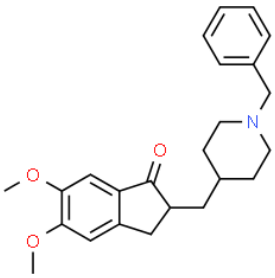

Figure 1 Donepezil

Source Chemspider, 2024.

Donepezil's function is to increase acetylcholine levels in the synaptic cleft by preventing the hydrolysis of the neurotransmitter in the brain. Therefore, its mechanism of action is related to the slowing down of the catabolism process of acetylcholine into choline and acetate by the enzyme acetylcholinesterase in the synaptic clefts. From this, Donepezil reduces general symptoms and maintains the cholinergic function of the central nervous system.[21,22] E2020 compensates for the cholinergic deficit by inhibiting acetylcholinesterase and, consequently, increasing acetylcholine in the synaptic cleft of the central nervous system. In addition, AChE-Is, including Donepezil, have neuroprotective effects, as they protect against glutamate excitotoxicity, neuronal damage and amyloid β (Aβ) neurotoxicity, due to the involvement of the phosphatidylinositol 3-kinase pathway.[23,24] As a result, Donepezil, through undetermined mechanisms, reduces neurodegeneration by associating the phosphatidylinositol 3-kinase pathway. In addition, it acts by improving social skills and cognitive functions, reducing memory loss and mitigating behavioral problems.[25,26]

Donepezil can be administered in orally disintegrating tablets in concentrations of 5 and 10 mg, transdermal in dosages of 5 and 10 mg and oral film-coated tablets in dosages of 5, 10 and 23 mg. Therefore, it has more convenient administration and dosage methods when compared to other ACHE-Is.[27,28] Regarding the pharmacokinetics of Donepezil hydrochloride, we can divide it into absorption, distribution, metabolism and excretion. First, Donepezil has a relative oral bioavailability of 100% and peak plasma concentration of 3 to 4 hours. Between the range of 1 to 10 mg, it has linear pharmacokinetics, without influence of food. To reach the steady state, 15 days are necessary, and, in this stage, the volume of distribution is 12 L/kg. Distribution is via the protein albumin and alpha-1 acid glycoprotein, even crossing the blood-brain barrier. Metabolism is performed by the liver via the enzymes CYP2D6, CYP3A4 and glucuronidation. The half-life is 70 hours. Excretion of Donepezil and its metabolites is via the kidneys and feces.[18,27-29]

In elderly individuals, absorption and excretion were unchanged when compared to younger individuals. However, an increase in distribution at steady state and a half-life of approximately 100 hours were noted, without requiring dosage adjustment.[27,30] Regarding hepatic metabolism, cytochrome P450 isoenzymes 2D6 and 3A4 also metabolize drugs such as antipsychotics, which can lead to several drug interactions. However, the affinity of isoenzymes 2D6 and 3A4 for Donepezil is low, which reduces such interactions. Thus, the most important drug interactions are the concomitant use of Donepezil and Tramadol or Donepezil and Bupropion, which increases the risk of seizures.[31,32] When associated with Neostigmine and Physostigmine, it increases the effects of Donepezil and with Phenytoin, Carbamazepine, Phenobarbital, Rifampicin and Dexamethasone, it decreases the effects of Donepezil. The interaction with Suxamethonium can prolong the effects of neuromuscular blocking agents and with Atenolol, Carvedilol, Metoprolol and Propranolol it can cause bradycardia.[28,33]

The main adverse effects are nausea, vomiting, muscle cramps, insomnia, dyspepsia, anorexia, weight loss, diarrhea and abdominal pain. However, they may present abnormal dreams, joint pain accompanied or not by stiffness and swelling, weight loss, blurred vision, edema, paresthesia, tachycardia and arrhythmia. There are reports of hypertension, hypotension, heart block, rhabdomyolysis and hepatotoxicity.[34,35]

Galantamine

Galantamine, approved in several countries for the symptomatic treatment of progressive neurodegenerative disorder –

Alzheimer's disease, Galantamine, a tertiary alkaloid that inhibits acetylcholinesterase and consequently increases the levels of the neurotransmitter acetylcholine, exhibits neuroprotective properties, acting as a scavenger of reactive oxygen species and reducing oxidative neuronal damage by preventing changes in membrane fluidity and protecting the mitochondrial membrane. It is an isoquinoline alkaloid, originated in the 1950s from Galanthus nivalis and Galanthus woronowii and was only approved for the treatment of Alzheimer's in Sweden in the 2000s and later in the European Union and the United States.[36]

Regarding its molecular characteristics, the drug is considered a tertiary alkaloid, exerting its therapeutic effect as a selective and reversible inhibitor of the enzyme acetylcholinesterase (AChE), differentiating itself from butyrylcholinesterase (BuChE). This specific interaction with AChE allows for an increase in the levels of acetylcholine (ACh), a crucial neurotransmitter in the central nervous system. In addition, Galantamine acts allosterically on nicotinic acetylcholine receptors, enhancing the action of agonists on these receptors. This additional activity contributes to modulating cholinergic neurotransmission, directly impacting cognitive function. Furthermore, its chemical structure is represented by the formula C17H21NO3, which can be seen in Figure II. These combined mechanisms position Galantamine as a significant therapeutic option in the treatment of neurodegenerative disorders, especially Alzheimer's disease.[37-39] (Figure 2).

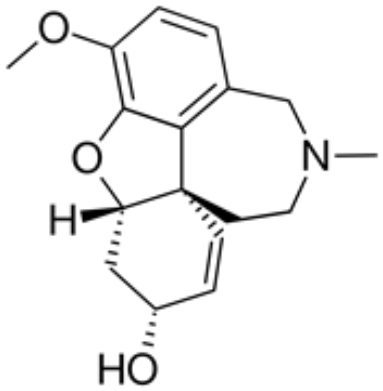

Figure 2 Galantamine.

Fonte Chemspider, 2024.

The mechanism of action of Galantamine is multifaceted, standing out mainly for its activity as an acetylcholinesterase (AChE) inhibitor and allosteric enhancer of nicotinic acetylcholine receptors (nAChRs).[40,41,48] Acetylcholinesterase (AChE) inhibition by Galantamine is characterized by its selective, reversible and competitive action on this enzyme. AChE is responsible for the degradation of the neurotransmitter acetylcholine (ACh) into acetate and choline. By inhibiting AChE, Galantamine prevents the rapid degradation of ACh, resulting in increased concentrations of this neurotransmitter in the synaptic cleft. This increased availability of ACh promotes more efficient cholinergic neurotransmission, potentially improving the cognitive deficits associated with Alzheimer's disease.[40,48]

Furthermore, Galantamine acts as an allosteric enhancer of nicotinic acetylcholine receptors (nAChRs), including the α4β2 and presynaptic α-7 subtypes. This interaction facilitates the release of acetylcholine from presynaptic neurons, intensifying the activation of nAChRs. The synergy between Galantamine and acetylcholine results in an amplification of the effects of cholinergic neurotransmission, contributing to the therapeutic effect observed in Alzheimer's disease.[41,48] These combined mechanisms increase the availability of acetylcholine in the brain, the main neurotransmitter involved in cognitive processes such as memory, thinking and learning. As a result, Galantamine demonstrates efficacy in the treatment of Alzheimer's disease, offering a promising therapeutic approach to improve cognitive function in patients affected by this neurodegenerative condition.[40,41,48]

Furthermore, Galantamine follows a linear pharmacokinetic pattern when used in doses between 8 and 32 mg daily, with an oral bioavailability of approximately 90%. After oral administration, the maximum concentration of Galantamine is normally reached in about one hour, and food intake can reduce this peak by 25% and delay it by 1.5 hours. Galantamine's ability to cross the blood-brain barrier is crucial to its therapeutic efficacy.[42,43,48] Galantamine is metabolized primarily in the liver, involving cytochrome P450 enzymes, glucuronidases, and urinary excretion in unchanged form. Inhibition of CYP2D6 and CYP3A4 enzymes may increase the oral bioavailability of Galantamine, and different metabolic pathways exist for extensive and poor metabolizers of CYP2D6.[42,43,48] Studies indicate that Galantamine extended-release capsules 24 mg, administered once daily, are bioequivalent to the immediate-release tablets 12 mg, administered twice daily. However, the extended-release capsules have lower peak concentrations and occur later. Age does not appear to have a significant impact on the pharmacokinetics of Galantamine, but CYP2D6 poor metabolizers may have increased exposure to the drug. Concomitant food intake does not significantly influence the pharmacokinetic parameters of Galantamine extended-release capsules. This detailed understanding of the pharmacokinetics of Galantamine is crucial to ensuring its clinical efficacy and safety, especially in patients with Alzheimer's disease and other conditions for which the medication is prescribed. [42,43,48]

It is worth noting that the most common adverse reactions include gastrointestinal effects, such as nausea, vomiting, diarrhea and abdominal pain, mainly due to the cholinergic action. Other effects include bradycardia, heart block, headache, dizziness and seizures, and it is essential to monitor patients, especially the elderly. Treatment requires care in titrating the dose and guidance on taking with food.[44,45]

It is extremely important to describe the possible drug interactions of Galantamine, the main ones are:

CYP2D6 and CYP3A4 inhibitors: Substances that inhibit these liver enzymes, such as ketoconazole, erythromycin, paroxetine, fluoxetine, and quinidine, may increase the oral bioavailability of Galantamine. This means that the concentration of Galantamine in the body may increase when administered concomitantly with these drugs, potentially leading to an increase inside effects.[46–48] H2-Receptor Antagonists: Coadministration of H2-receptor antagonists, such as cimetidine, may increase the bioavailability of Galantamine. This is because these drugs may interfere with the hepatic metabolism of Galantamine, leading to higher plasma levels of the drug.[46–48]

Hepatic Enzyme Inducers: Drugs known to induce hepatic cytochrome P450 enzymes, such as carbamazepine, phenytoin, phenobarbital, rifampin, and dexamethasone, may accelerate the metabolism of Galantamine. This may result in a decrease in the plasma concentration of Galantamine and a reduction in its therapeutic efficacy.[46–48] It is important to closely monitor patients who are receiving Galantamine treatment and are also using any of these medications, adjusting doses as necessary to ensure the effectiveness of treatment and to avoid unwanted side effects.[46–48]

Memantine

Memantine, approved by the Food and Drug Administration (FDA) and used in the treatment of Alzheimer's disease, acts as an antagonist of the glutamate receptor subtype of the N-methyl-D-aspartate receptor (NMDAR). It blocks this subtype (NMDAR) of glutamate receptors (the main excitatory neurotransmitter in the human brain), preventing the hyper activation of glutamine receptors and facilitating normal activity. In addition, it plays a fundamental role in synaptic plasticity, which is a neuronal mechanism believed to be the basis of memory formation. NMDA receptors are involved in a process called excitotoxicity that plays a role in the pathophysiology of Alzheimer's disease. It is noted that, with a variable level of evidence, memantine is also widely used off-label for mild AD, requiring prior clinical judgment and evaluation of psych pharmacotherapy data for appropriate use. In conclusion, this drug delays the neurotoxicity involved in Alzheimer's disease and other neurodegenerative diseases.[49-52]

Memantine (Figure 3) is a primary aliphatic amine derived from the 3,5-dimethyl derivative of 1-aminoamdamantane, represented in Figure III. It has a nucleus similar to amantadine, has the chemical name of 1-amino-3,5-dimethyladamantane hydrochloride and molecular form C12H21N, having an average mass of 179,302 Da and molecular weight of 215.76 g.[53] (Figure 3).

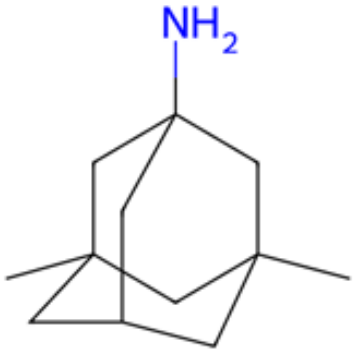

Figure 3 Memantine.

Fonte Chemspider, 2024.

As previously mentioned, memantine is a non-competitive antagonist of NMDA receptors, voltage-dependent cation channels, allowing their physiological activation during memory formation processes, but blocking the opening of the channels and their pathological activation. This occurs through the rapid (voltage-dependent) effects of the drug's interactions with NMDA receptors. Its action under physiological conditions can be compared to magnesium ions, as it can block NMDA receptors in the resting state and, like magnesium, is displaced from its binding site under physiological activation conditions; however, it cannot detach from the receptor during pathological activation.[54-56]

In short, it has a neuroprotective action against the excitotoxic activation of glutamate receptors, that is, it neutralizes excessive stimulation by reducing the influx of calcium into the cells. It is worth noting that the glial cells of the brain contain glutamate transporters that help maintain the transmembrane gradient of sodium (Na +) and potassium (K +) ions. Calcium plays a critical role in the pathology of dementia, inducing neuronal cell death induced by excitotoxicity and hyperphosphorylation of tau proteins. Furthermore, memantine also exhibits antagonist activity at type 3 serotonergic (5-HT3) and nicotinic acetylcholine receptors. However, it has no activity at gamma-aminobutyric acid (GABA), benzodiazepine, dopamine, adrenergic, histamine or glycine receptors or at voltage-gated calcium, sodium or potassium channels. Like other NMDA receptor antagonists, at high concentrations it can inhibit synaptic plasticity mechanisms. However, it has been found in animal models that at lower, clinically relevant concentrations it can promote synaptic plasticity and preserve or improve memory. Formulations are available as oral tablets, extended-release capsules, and oral solutions (2-20 mg).[54,56]

In most cases, memantine is tolerated when administered orally, which has demonstrated good clinical efficacy in several randomized studies. Through this administration, the drug is absorbed from the gastrointestinal tract following a linear pharmacokinetic profile. It is partially metabolized in the liver. The hepatic microsomal enzyme system, specifically CYP450, does not impair the degradation of memantine. The peak plasma concentration of memantine occurs approximately 9 to 12 hours postdose after multiple doses of memantine hydrochloride extended-release capsules. However, maximum plasma concentrations are reached approximately 18 hours and 25 hours after administration with food and on an empty stomach, respectively. Two doses (10 mg) are required to complete the usual daily dose of 20 mg. Elimination is primarily renal, with an elimination half-life of 60 to 80 hours. About 48% of the elimination is unchanged.[49,54]

The remaining 48% is transformed into polar metabolites with minimal NMDAR antagonist activity. Metabolites include the N-glucuronide conjugate, 6-hydroxymemantine, and 1-nitroso-deaminated memantine. 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. Renal clearance involves active tubular secretion moderated by pH-dependent tubular reabsorption.[49,54]

Drug interactions may occur, causing alkaline urine (reducing memantine clearance by approximately 80%, leading to drug accumulation) and increased neuropsychiatric adverse effects in the case of combination with other NMDA antagonists; caution is required when administering memantine in combination with amantadine or dextromethorphan, due to possible interactions that may increase adverse effects. The most common adverse effects of memantine in clinical trials are dizziness, headache, confusion, diarrhea, and constipation. Additional effects include fatigue, pain, hypertension, weight gain, hallucinations, confusion, aggressive behavior, vomiting, abdominal pain, and urinary incontinence. Uncommon effects also occur in the following systems: Neurological, Cardiovascular, Endocrine, Gastrointestinal, Hematological, Hepatic, Renal, Respiratory, Dermatological, Musculoskeletal, among others. The use of memantine and donepezil together was analyzed in a study for a period of 6 months, patients presented gastrointestinal adverse effects.[55,57,58]

In contrast, a 2018 experimental study on the efficacy and safety of memantine treatment for AD found that memantine had little efficacy on AD symptomatology and the safety profile was similar to placebo. No evidence of improvement in discontinuation of memantine treatment was found, indicating an uncertain risk-benefit ratio. No intervention characteristic or patient subgroup clearly showed a significantly better risk-benefit ratio.[59,60]

Rivastigmine

Rivastigmine, also known as ENA-713, is an anticholinesterase drug. It has a preference for inhibiting acetylcholinesterase in the

brain, acting primarily in the hippocampus and cerebral cortex, regions affected by Alzheimer's disease. Early results suggest that doses between 6 and 12 mg per day may bring clinical improvements, although common side effects include headache, nausea, dizziness and intestinal problems. There is still much uncertainty about its efficacy and safety due to the lack of available information. However, the FDA approved its marketing in 2000 to treat mild to moderate Alzheimer's.[61,62]

In the context of its molecular properties, rivastigmine is characterized as a pseudo-irreversible inhibitor of both acetylcholinesterases and butyrylcholinesterases, with a propensity to exhibit low protein binding affinity. It is important to note that rivastigmine has a specificity for the G1 form of acetylcholinesterase, which is predominantly found in the brains of patients with Alzheimer's, suggesting a possible therapeutic benefit. Furthermore, its prolonged duration of action and its ability to cross the blood-brain barrier make it a viable alternative for the treatment of dementia.[63,64] Alzheimer's disease (AD) is a neurodegenerative condition associated with a reduction in cholinergic neurotransmission, resulting in cognitive deficits. These deficits are partly attributed to decreased levels of acetylcholine (ACh) in the brain. To address this deficiency, acetylcholinesterase (AChE) inhibitors have been widely used in the treatment of AD. Rivastigmine is one such inhibitor that has demonstrated efficacy by acting on both AChE and butyrylcholinesterase enzymes. (BuChE).[65,67,68]

AChE, found predominantly at synaptic nerve junctions and in areas of high activity in the cerebral cortex, is responsible for the degradation of ACh. On the other hand, BuChE is present in brain glial cells and plays a role in the regulation of cholinergic activity. With aging and in pathological conditions such as AD, an increase in the activity of these cholinesterase enzymes is observed, contributing to the reduction of ACh levels. Rivastigmine acts differently from other cholinesterase inhibitors by reversibly binding to and inhibiting both AChE and BuChE. This mechanism of action results in an overall increase in ACh levels in the brain. Specifically, rivastigmine carbamylates the ester site of AChE with its carbamate moiety, leading to prolonged inhibition of the enzyme. Furthermore, rivastigmine exhibits selectivity by preferentially inhibiting the monomeric (G1) form of AChE compared to the tetrameric (G4) form. This selectivity may be beneficial in the treatment of AD, where the G1 form is more involved in ACh degradation. By increasing ACh levels in the brain, rivastigmine promotes an amplification of cholinergic activity, which is essential for adequate cognitive functioning. Furthermore, rivastigmine also exerts additional neuroprotective effects, possibly influencing brain levels of amyloid-beta (Aβ), which are implicated in the pathogenesis of AD.[65,66-68]

Absorption of Rivastigmine after oral administration is rapid and complete, with peak plasma concentrations reached within approximately one hour.[69] This process is influenced by the presence of food in the gastrointestinal tract, and absorption may be reduced when administered with food.[70] After being absorbed, Rivastigmine is extensively metabolized in the liver, mainly by the enzyme pseudo cholinesterase, resulting in inactive metabolites.[71] Studies have shown that pseudo cholinesterase activity can vary between individuals, thus affecting the rate of metabolization of rivastigmine and its plasma concentrations.[72] Rivastigmine is widely distributed throughout the body, crossing the blood-brain barrier and reaching the central nervous system, where it exerts its therapeutic activity.[73] Rivastigmine's binding to plasma proteins is moderate, around 40 to 55%.[74] The elimination of rivastigmine and its metabolites occurs mainly via the renal route, with approximately 97% of the administered dose being excreted in the urine, mainly in the form of metabolites.[75] The elimination half-life of rivastigmine varies between 1 and 2 hours, while that of the metabolites is longer, around 3 to 5 hours.[76]

The pharmacokinetics of rivastigmine may be affected by several factors, such as advanced age, hepatic or renal dysfunction, and concomitant use of drugs that affect cholinesterase metabolism[77]. Therefore, it is important to consider these aspects when prescribing rivastigmine to optimize its efficacy and minimize the risk of adverse events. In summary, rivastigmine has well-characterized pharmacokinetics, with rapid absorption, extensive metabolism in the liver, wide distribution throughout tissues, and mainly renal elimination. However, interactions with other drugs and the patient's clinical conditions may influence its pharmacokinetic profile, and it is essential to monitor its use on an individual basis.[77-79] It is not advisable to use metoclopramide and rivastigmine together due to the risk of an additive extrapyramidal effect. On the other hand, coadministration of metoclopramide and rivastigmine with other cholinomimetic drugs may cause additional adverse effects. In addition, rivastigmine may reduce the side effects of anticholinergic drugs such as oxybutynin and tolterodine, interfering with their activity. This drug may also increase the effects of muscle relaxants during anesthesia, increasing the risk of complications such as bradycardia when used in conjunction with beta-blockers such as atenolol. Pharmacodynamic interactions with other types of drugs, such as antipsychotics and cholinergic, may also occur. On the other hand, cholinesterase inhibitors can generally be used safely in conjunction with other drugs.[77-79]

Methodology

This is a systematic review study carried out in the period covered that followed the recommendations of the preferred reporting items for systematic reviews. Thus, using electronic databases as a resource, using the main scientific data repositories: Pubmed, Science direct, Scopus and Web of science. The keywords used were: Rivastigmine, Donepezil, Galantamine, Memantine, Alzheimer's disease. The terms were searched separately and also combined. The research was carried out between the months of January and September 2024.

We selected 79 articles following exclusion and inclusion criteria for pharmacological treatment of Alzheimer's disease, and gave priority to publications from the last ten years.

Results

Table 1 Pharmacokinetics of drugs used in the symptomatic treatment of AD (Table-1[18, 27-30, 42, 43, 46-49, 54, 56, 69-72, 74-76])

Drug	Absorption	Distribution	Metabolization	Excretion
Memantine	peak plasma concentration occurs approximately 9 to 12 hours after the dose, there is no divergence in the way of ingestion	Plasma protein binding is 45% with a mean volume of distribution of memantine of 9 to 11 L/kg	Partially metabolized in the liver. Degradation is not significantly affected by the hepatic microsomal enzyme system (CYP450)	The elimination half-life is approximately 60 to 80 hours. Approximately 48% is excreted in the urine unchanged, the remainder is transformed into metabolites.
Rivastigmine	Absorption of rivastigmine after oral administration is rapid and complete, with peak plasma concentrations reached within approximately one hour.	Rivastigmine is widely distributed throughout the body, crossing the blood-brain barrier and reaching the central nervous system.	rivastigmine is metabolized in the liver, mainly by the enzyme pseudocholinesterase, resulting in inactive metabolites	occurs mainly via the renal route, with approximately 97% of the administered dose being excreted in the urine, mainly in the form of metabolites
Galantamine	Absorbed mainly in the gastrointestinal tract, with high oral bioavailability. After oral administration, it reaches maximum concentration in the blood in about one hour, and may be affected by food intake.	Galantamine is distributed throughout the body after absorption, crossing the blood-brain barrier to reach the brain, where it exerts its therapeutic effects..	The primary metabolism of galantamine occurs in the liver, involving cytochrome P450 enzymes and glucuronidases. After metabolism, galantamine is excreted mainly in the urine in unchanged form. Inhibition of CYP2D6 and CYP3A4 enzymes may increase its oral bioavailability.	After hepatic metabolism, galantamine is mainly excreted in the urine in unchanged form. Inhibition of CYP2D6 and CYP3A4 enzymes may influence excretion and increase its oral bioavailability.
Donepezil	Relative oral bioavailability of 100% and peak plasma concentration of 3 to 4 hours	Distribution is via the protein albumin and alpha 1 acid glycoprotein, crossing the blood-brain barrier.	Metabolism is carried out by the liver through the enzymes CYP2D6, CYP3A4 and glucuronidation. The half-life is 70 hours.	Donepezil and its metabolites are excreted via the kidneys and feces.

Source Author himself.

Table 2 Drug Interactions (Table-2 [28, 31-33, 46-48, 55, 57, 58, 77-79])

Drug	Major Drug Interactions	
	Drug	Effect
Memantine	Acetazolamide	The use of Acetazolamide may lead to drug accumulation, resulting in the risk of adverse effects.
	Amantadine, Ketamine and Dextromethorphan	The use of Amantadine, Ketamine and Dextromethorphan may increase neuropsychiatric adverse effects, but studies indicate that combined use can be done with caution.
	Atenolol, bisoprolol	Additive effects leading to bradycardia (may result in syncope)
Rivastigmine	Succinylcholine	Rivastigmine may potentiate the effects of succinylcholine-type muscle relaxants during anesthesia.
	Metoclopramide	Considering the possibility of an additive extrapyramidal effect, the concomitant use of metoclopramide and Rivastigmine is not recommended.
Galantamine	Ketoconazole, Erythromycin, Paroxetine, Fluoxetine, Quinidine.	They inhibit the liver enzymes CYP2D6 and CYP3A4, which are involved in the metabolism of Galantamine. They reduce the rate at which the body metabolizes Galantamine. This results in a greater amount of Galantamine being available in the body, which may increase the side effects associated with Galantamine, such as nausea, vomiting, diarrhea, and abdominal pain.
	Cimetidine	It is an H2 receptor antagonist and may interfere with the hepatic metabolism of Galantamine. This leads to a decrease in the rate at which the body metabolizes Galantamine, resulting in higher plasma levels of Galantamine. As a result, there may be an increase in the effects of Galantamine in the body.
	Carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone.	They induce hepatic cytochrome P450 enzymes, which are involved in the metabolism of Galantamine. When given together with Galantamine, they increase the rate at which the body metabolizes Galantamine. This results in lower plasma levels of Galantamine, which may reduce its therapeutic efficacy in the treatment of Alzheimer's disease.
	Tramadol and Bupropion	Seizure risk
DONEPEZIL	Neostigmine and Physostigmine	Increases the effect of Donepezil
	Phenytoin, Carbamazepine, Phenobarbital, Rifampicin and Dexamethasone	Decreases the effect of Donepezil
	Suxamethonium	Prolong effects of neuromuscular blocking agents
	Atenolol, Carvedilol, Metoprolol and Propranolol	Bradycardia

Source Author himself.

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Table 3 Adverse effect (Table-3 [34, 35, 44, 45, 55, 57, 58, 61, 62])

Drug	Adverse effect
Memantine	Most common reactions: Dizziness, headache, confusion, diarrhea and constipation
Rivastigmine	the main adverse effects are gastrointestinal and the main symptoms are nausea and vomiting
Galantamine	Nausea, vomiting, diarrhea, and abdominal pain, mainly due to cholinergic action. Other effects include bradycardia, heart block, headache, dizziness, and seizures and monitoring of patients, especially the elderly, is essential.
Donepezil	Nausea, vomiting, dyspepsia, anorexia, weight loss, diarrhea, and abdominal pain

Source Author himself

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Conflicts of interest

The authors declare to have no conflict of interest.

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