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REVIEW ARTICLE

Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment

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Abstract: Dementia is characterized by the impairment of cognition and behavior of people over 65 years. Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in the world, as approximately 47 million people are affected by this disease and the tendency is that this number will increase to 62% by 2030. Two microscopic features assist in the characterization of the disease, the amyloid plaques and neurofibrillary agglomerates. All these factors are responsible for the slow and gradual deterioration of memory that affect language, personality or cognitive control. For the AD diagnosis, neuropsychological tests are performed in different spheres of cognitive functions but since not all cognitive functions may be affected, cerebrospinal fluid biomarkers are used along with these tests. To date, cholinesterase inhibitors are used as treatment, they are the only drugs that have shown significant improvements in the cognitive functions of AD patients. Despite the proven effectiveness of cholinesterase inhibitors, an AD carrier, even while being treated, is continually subjected to progressive degeneration of the neuronal tissue. For this reason, other biochemical pathways associated with the pathophysiology of AD have been explored as alternatives to the treatment of this condition such as inhibition of β-secretase and glycogen synthase kinase-3β. The present study aims to conduct a review of the epidemiology, pathophysiology, symptoms, diagnosis and treatment of Alzheimer's disease, emphasizing the research and development of new therapeutic approaches.

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1. INTRODUCTION

Dementia is characterized by impairment of cognition and behavior of people over 65 years of age. Alzheimer's disease (AD) is the neurodegenerative disorder most prevalent in the world, affecting about 24 million people and it is estimated that by 2050 this number will be quadrupled. Its main features are the deposit of β-amyloid (Abeta) peptides in the extracellular surface of neurons and the formation of neurofibrillary tangles arising from the intracellular accumulation of hyperphosphorylated Tau protein.

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AD is also associated with the deficit of the neurotransmitter acetylcholine (ACh) and oxidative stress caused by exacerbation of glutamatergic transmission [1-5]. In this review we will discuss the epidemiology, pathophysiology, diagnosis, symptoms and prospects for new pharmacological treatments for AD.

2. EPIDEMIOLOGY

Estimates in 2015 showed that around 46.8 million people are affected by dementia worldwide. This number of new cases is almost 30% (9.9 million new cases) greater than the incidence presented in the report of the World Health Organization (WHO) in 2010. The highest incidence rates were in Asia (49%), Europe (25%) and America (18%) [6, 7].

The prediction is that, by the year 2030, the number will reach 74.7 million people and 131.5 million in 2050. Also, according to the estimates by the World Alzheimer Report 2015 [6], East Asia and Africa are the regions with the largest number of people with dementia (about 9.8 million people), followed by Western Europe with 7.4 million affected [6].

According to the Diagnostic and Statistical Manual of Mental Disorders (2014) [8], the AD has a progressive increase proportional to aging. Thus, the age is considered to be a prevalence factor. Epidemiologically, AD affects approximately 5% of individuals over 65 years and 20% of those over 80 years. This means that the rate of prevalence doubles every 5 years [9]. The World Alzheimer Report (2015) [6] pointed out that in Europe and the Americas the highest incidence of AD is between 80-89 years, in Asia among those aged 75-84 years and 65-74 years in Africa.

Each year, in the United States, there is an increase in the prevalence of AD in military veterans who have suffered traumatic brain injury (TBI), post-traumatic stress disorder and/or injuries associated with military service [10]. These increasing infirm military veterans tend to exacerbate hospital costs because of the need for medical care and/or hospitalization for long periods. In the wars of Iraq and Afghanistan, about 23% of cases of TBI were originated from improvisation with explosives [11].

People who have had moderate to severe TBI have a two- to four-time higher risk to develop AD at older ages [12]. A correlation with dementia development in boxers was also observed [13]. But other sports of much contact and strength, such as American football and hockey, lead such athletes to TBI (about 1.6 to 3.8 million affected annually) in the United States [14-16].

The census of 2012 indicated that the population obtained a substantial increase in the elderly population. One indicator in this regard is the aging index, which is the ratio of the number of people aged over 60 for every 100 people under 15 years old. The rate in Brazil is around 51.8, therefore the data show that there is a person aged 60 years or older for every two people under 15 years old [17]. In Brazil, more concrete data on the AD come from the 2000s, when the statistical bases of the country compared with data from other regions revealed the prevalence in the country of 1.2 million cases, and the incidence of 100,000 new cases each year [18]. However, there is need to improve the search and registration of the data, since the AD may be unregistered or underdiagnosed [19, 20].

According to the World Alzheimer Report 2015 [6], the overall costs of the disease (medical care, social care and informal care) were 818 billion dollars with an increase of 35.4% compared to the same study in 2010 [7]. The trend of the cost with Alzheimer's disease for 2018 will be $ 1 trillion, rising to 2 trillion in 2030 [6].

3. PATHOPHYSIOLOGY

Even with over a hundred years of history, the AD does not have full clarification regarding its pathogenesis and still lacks a therapy that induces a natural healing. Nevertheless, macroscopic and microscopic markers related to it are known and may help in its characterization, in understanding of the disease pathogenesis and in the development of possible strategies [21, 22].

At the macroscopic level (Fig. **1**) there is the atrophy of the hippocampus and cerebral cortex, which in AD appears more sharply due to age [23, 24]. Microscopically it is possible to observe the formation of amyloid plaques, or senile plaques, which are amorphous structures of Abeta, and accumulation of hyperphosphorylated Tau protein which implies the formation of neurofibrillary tangles, and extensive neuronal loss [25-30].

Recent research showed other mechanisms are related to the formation of these AD markers, ranging from genetic imprint factors [30, 32] as family heritage [33], and mechanisms that involve apolipoprotein E [27, 31, 34], the mechanism of oxidation processes [25, 35] culminating in the neurodegeneration process.

3.1. Genetic Mechanism

The vast majority of AD case occurrences are sporadic, *i.e.* where there is no dominant genetic cause, but rare mutations may occur in the APP gene, originating

the familiar AD [33], and allele ε4 of apolipoprotein E (ApoE) that has been shown in recent studies as the strongest genetic risk factor related to AD development process [27, 31].

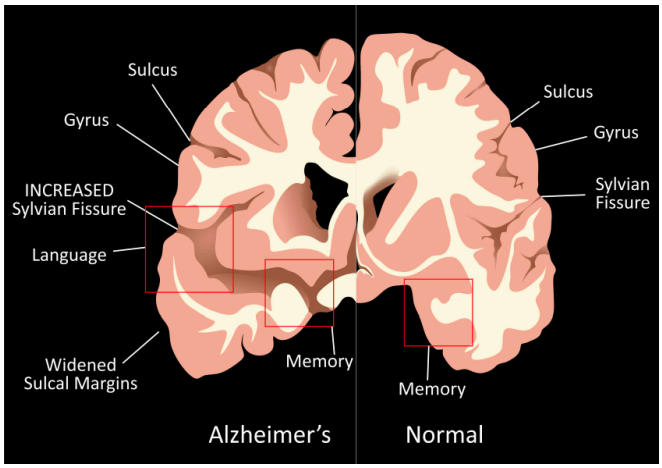

Fig. (1). Macroscopic changes. Atrophy of the hippocampus and cerebral cortex.

The human carriers of ApoE are present in approximately 1 of every 5 individuals. The subsidy that ApoE provides to the development of AD is realized when it is observed that these individuals account for about 65% of cases of the disease [31] and that carriers of the ApoE have the risk of developing Alzheimer's increased three fold [32]. The mechanisms that correlate the presence of ApoE with AD are not well understood yet, however, it is being suggested that in such cases there is a decrease in clearance of Abeta in the brain [31, 36].

In addition to the mechanism involving ApoE, studies also demonstrate a strong correlation between the presence of preselinin alleles (PSEN 1 and PSEN 2) in AD-patients and in individuals with a tendency to be carriers of AD or other related diseases [37, 38]. There is precedence in literature of the identification of two different types of mutation in this gene in patients with familial AD [39, 40].

PSEN 1 and PSEN 2 genes are rare in individuals with AD, although their relationship with ApoE is a major factor when the disease is due to genetic causes. They are involved in early-onset pathology, which is a rare form of the disease [41]. Mutations in PSEN 1 (chromosome 14) account for 18% to 50% of these early onset cases [42], mutations in PSEN 2 (chromosome 1) have been rarely reported and was mostly detected in African populations and in European countries [43]. The mechanism of correlation between preselinin and the control of APP cleavage has not yet been fully elucidated [44].

3.2. Amyloid hypothesis and Protein Tau

As previously mentioned, the Abeta fragments and neurofibrillary tangles are important markers for AD [25-27] which characterize the amyloid hypothesis. These deposits are the result of the wrong folding of native proteins, *i.e.* forming after altered cleavage of the amyloid precursor protein (APP) [45-47].

APP is a transmembrane glycoprotein with approximately 770 amino acids expressed by several cells, including CNS neurons [47, 48]. The cleavage of APP occurs through the enzymes α-, β- and ɣ-secretase [44, 49], while the amyloid pathway has its cascade unleashed when APP is cleaved by β-secretase thereby forming insoluble peptides having 39 to 43 fragments [47, 48, 50].

The Abeta fragments, especially the Abeta-42 isoform, have pronounced cytotoxic properties which are related to the process of neurodegeneration, for facilitating the formation of oxiradicals [51], being or not directly toxic to neuronal cells, by deregulating calcium homeostasis due to lipidic dysregulation of the cell membrane [26, 27, 36, 37, 52], these fragments form the insoluble structures that characterize histopathologically the AD (senile plaques) and this process ends up leading to neuronal death [53, 54].

Tau protein promotes a kind of assembly of tubulin, providing microtubule stability [33]. Neurofibrillary tangles are the result of Tau protein hyperphosphorylation. According to the results presented in the work of Stancu and co-workers, although mice models that express the mutant amyloid precursor protein without tau overexpression did not show neurofibrillary tangles, subtle changes in mice endogenous Tau were induced by high concentrations of Abeta, resulting in the process of hyperphosphorylation of Tau [27]. Research has also found strong evidence of the interdependence between Aβ accumulation and tau protein aggregation, which represents the final stage of disease pathogenesis [55, 56].

3.3. Inflammatory Mechanism and Mitochondrial Dysfunction

AD is a disease that is closely linked to inflammatory processes [41, 57]. In addition, several studies have shown that Tau pathologies are drastically exacerbated during the occurrence of acute and chronic inflammatory processes [27, 58-60]. Those inflammatory processes are mediated or induced by microglial clusters around the densest regions of Abeta plaques, by high levels of pro-inflammatory cytokines and by mi-

croglial activation that precedes the formation of neurofibrillary tangles (Fig. **2**) [41].

With regard to mitochondrial dysfunction, it is believed that the deposit of Abeta fragments and pathological Tau protein affect mitochondrial function in brain cells, specifically in regard to the impairment of mitochondrial oxidative metabolism [27, 35, 61]. Studies related to the presence of Abeta peptides carried out by Benevento enabled him to conclude, with more specificity, that these peptides can be directly toxic to neuronal mitochondria [61].

3.4. Oxidative Stress

Studies show that there is strong evidence that oxidative stress induced by Abeta is crucial to the pathogenesis and progress of AD [26], being present, both as cause and consequence, of inflammatory processes in general, which is characteristic of neurodegenerative diseases [62].

The brain is an organ that has high energetic activity, this energy demand is supplied by mitochondrial oxidative phosphorylation, and this process can lead to the formation of highly reactive oxygen species [63]: oxidative stress is a result of excessive production of these species. In this case, the protective mechanisms are compromised, the reactive oxygen species begin to accumulate and the neurons become susceptible to the excitotoxic lesion [47]. However, this mechanism depends on Abeta fragments which, when accumulated, promote the reduction of iron and brain copper, which are key factors to trigger oxidative stress [64] which, under these conditions, promotes DNA damage [25].

3.5. Cholinergic Hypothesis

Among the mechanisms related to the onset and evolution of AD, a extremely studied hypothesis is the cholinergic hypothesis, which was the first theory related to AD pathogenesis [54, 64].

In general, the brain of AD carriers presents, in addition to the histopathological markers previously described, atrophy, synaptic loss and deficiency in central neurotransmission. There is overall degeneration of basal forebrain neurons [65]. In the beginning of the disease there is loss of the cholinergic neurons in the basal nucleus and in the entorhinal cortex, but in the advanced stage of AD, more than 90% of the cholinergic neurons of the basal nucleus are lost [66].

Bartus and Emerich (1999) [67] point out that according to the cholinergic hypothesis, the abnormal or impaired functioning of the cholinergic system proves

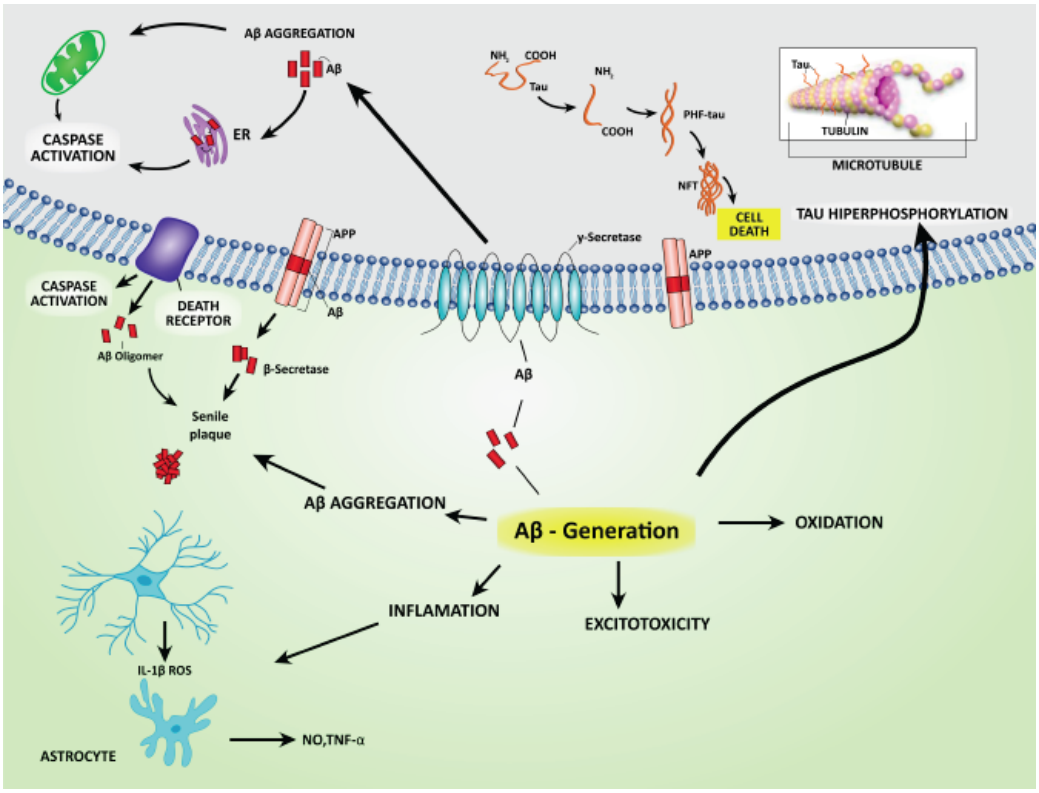

Fig. (2). Amyloid cascade in AD.

capable of inducing a memory deficiency in animal models, similar to AD. According to this hypothesis, the destruction of cholinergic neurons in the basal forebrain and the loss of central cholinergic transmission leads to the appearance of cognitive and non-cognitive symptoms in patients with AD [66].

It is also observed that the cholinergic hypothesis is also characterized by: a marked decrease in acetyltransferase concentration responsible for the synthesis of acetylcholine in the cortex and hippocampus; and due to the loss of cholinergic neurons in the Meynert basal nucleus [68]. The cholinergic hypothesis also corroborates that the dysfunction and cell death of neurons responsible for the maintenance of specific transmission systems leads to the deficiency of Ach, noradrenaline and serotonin [69].

4. SYMPTOMATOLOGY

AD is often a major cause of dementia in elderly people, when the evolution of the symptoms becomes severe, with slow and gradual deterioration of the memory that affects language, personality and cognitive control [70-74]. AD has major medical, economic and social consequences due to problems such as dementia, dependency and disability [75].

AD can be classified in three stages: the early stage, where the loss of memory is discrete; cholinergic neurons in the limbic system are affected, the hippocampus shrinks by approximately 25% of its volume. The light declines in memory capacity are associated with damaged neurons since they are responsible for the short and long term memory; the intermediate stage, which is characterized by difficulty in recognizing and communicating with people, is a long stage and can last from two to ten years according to Seidl [76]. After that, there is a decline in the acetylcholine levels of some neurons, among these are those located in the ventral telencephalon, which under normal conditions are involved in information storage and long-term memory; and the final stage, in which the patient is completely debilitated and there is total dependency and inability to perform daily activities. Additionally, no information recovery is possible due to the interference of the disease in the limbic system. The destruction of stored memories are associated with degeneration of cholinergic neurons throughout the cerebral cortex. The person forgets his past, friends and family. This phase lasts from one to three years on average and ends with the death of the patient [77-82].

According to Petronilho, this condition is mainly associated to the reduction of acetylcholine (ACh) levels in the synaptic process, since this neurotransmitter is directly related to cognitive, motor and memory processes [83]. In the early stages of AD there are typical behavioral changes such as irritability and indifference in family affairs or entertainment [71]. Patients show personality changes, confusion, anger, sadness, lack of direction and difficulty in concentrating. Agitation is associated with loss of volume in several specific areas of the brain, including the frontal cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula, amygdala and hippocampus. There are two different mechanisms that explain the agitation in AD, one is due to emotional regulation deficits (emotional responses) and another is due to executive function deficits (problem solving). However, it is important to state that their evolution may vary from patient to patient [84].

Over time, more than 90% of all patients feel symptoms such as apathy, restlessness, anxiety, depression, hallucinations, delirium, motor activity abnormality, irritability, sleep disorders, eating disorders, euphoria or disinhibition. Mood disorders affect a significant percentage of individuals who develop AD at some point in the evolution of dementia. Depressive symptoms are observed within 40-50% of patients, while depressive disorders affect about 10- 20% of cases. Depressive symptoms are very common in AD, major depressive disorder has been extensively studied as a possible neurocircuitry disorder, but there are still very few neuroimaging data published involving depression in AD [84-88].

AD patients develop a gradual and insidious cognitive deficit that becomes disabling in advanced stages of the disease. These devastating symptoms compromise significantly the quality of life of patients, leading to absolute dependence, hospitalization and inevitably death [77, 89-91].

5. DIAGNOSIS

The diagnosis of AD performed in an initial stage of the disease is essential to ensure that the patient has good living conditions [92]. For this, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and established standards by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) concomitant with Alzheimer's Disease and Related Disorders Association (ADRDA) are used [93]. These neuropsychological tests and psychometric tests, in various fields, analyze the cognitive functions of patients. In addition, blood tests, structural neuroimaging, molecular and functional neuroimaging,

cerebrospinal fluid, electroencephalogram (EEG) and evoked potentials are performed. Genetic studies are also important complementary tests that can integrate a more complete diagnosis of the disease [94].

For global cognitive function, the main clinical examination established by NINCDS-ADRDA is the Mini-Mental State Examination (MMSE). The MMSE is one of the most used tests in the world. It was prepared by Folstein *et al.,* [94]. This test can be used alone or coupled with other tools to assess the cognitive level of the patient [95]. Nitrini and colleagues [96] recommend the association of Information - Memory - Concentration Test (IMC) of Blessed [97] and The Cognitive Abilities Screening Instrument - Shortform [98] for ratification of the reduction in global cognitive framework.

In the memory assessment, delayed recall tests can be used [99], the Rey Auditory Verbal Learning Test (RAVLT) [100] or the memory logic of the Wechsler Memory Scale (WMS) [101]. In this aspect, exams in Brazil also use a battery of neuropsychological delayed recall of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [102].

Analyzing the cognitive function of attention, the most applied exams are random letter Test [103], Digit Extension (direct and reverse) and the Trail Making Test [104].

To check the cognitive framework of language the instrument ADAS-cog is used, naming real objects [105]; Boston Naming Test (BNT) that applies the name of 15 figures in black and white [106] or designating eight figures in the Abbreviated Neuropsychological battery test (NEUROPSI) [107].

Regarding conceptualization and abstraction, the Cambridge Examination for Mental Disorders Similarities Test of the Elderly (CAMDEX) [108] or NEUROPSI [109] are tests that require the ability to relate three pairs of nouns.

In constructive skills, the patient is examined by the Clock Drawing Test (CDT) [110] and geometric designs of CERAD [102].

However, these neuropsychological tests have become deadlocked by the new proposals of clinical manifestations, such as mild cognitive impairment (MCI) [111]. Loss of timely memory and cognitive changes in routine cases can be common and not necessarily an early development of AD, as many activities are still preserved [111, 112]. From this context, it is necessary that additional tests reinforce the diagnosis of AD [113].

Laboratory blood tests for diagnosis of AD should include the following parameters: complete blood count, serum urea, creatinine, thyroxine (T4), thyroid stimulating hormone (TSH), albumin, liver enzymes (SGOT, SGPT, gamma GT), vitamin B12, calcium, serologic tests for syphilis and in patients younger than 60 years, complete HIV serology [114].

Computed tomography (CT) and magnetic resonance imaging (MRI) are important structural neuroimaging exams. CT reveals subdural hematomas, tumors or normal pressure hydrocephalus. However, depending on the clinical history of the patient, these may be causes of reversible dementia [94]. Therefore, brain MRI details more accurately change in areas of the cerebral cortex and hippocampus [106].

Cerebrospinal fluid exams analyze the changes in two biomarkers: reduced Abeta protein 1-42 (Abeta42) which is a component of neuritic plaques and increased levels of Tau protein (total and phosphorylated) that is related to neuronal decay [115-117].

The positron emission tomography (PET) identifies markers of β-amyloid plaques (pathological signature) deposited in neuronal tissue [118]. The tomography single photon emission computed tomography (SPECT) is used for differential diagnosis of dementia, including depression of the elderly and differential diagnosis of Alzheimer's disease and dementia through Lewi bodies (generalized in the cortex) [119].

In addition, there are molecular diagnostics associated with magnetic resonance spectroscopy (MRS). MicroRNAs (miRNA), small non-coding RNAs that regulate gene expression at post-transcriptional level, have been applied to the diagnosis of AD [120]. Changes in miRNA network caused by the disease, contribute to deregulation of genes of the amyloidogenic cascade (genes such as APP, BACE1 and MAPT) [121].

6. PHARMACOLOGICAL TREATMENT

6.1. Acetylcholinesterase Inhibitors

To date, cholinesterase inhibitors (Table **1**) are the only drugs that have shown significant improvements in the cognitive process of patients with AD, to reduce their symptoms by improving the cholinergic function in neuronal synapses [122,123]. These drugs act as inhibitors of cholinesterase (Acetylcholinesterase - AChE, and butyrylcholinesterase - BChE), which are enzymes responsible for degradation of the neurotransmitter acetylcholine (ACh) in the synapses, after transmission of the nervous impulse. Thus, to inhibit

them, cholinesterase inhibitors increase the availability of these neurotransmitters in the synaptic cleft, reducing the symptoms of AD [123].

In this context, many studies have been conducted in order to discover new drugs that act in this pathogenic pathway. However, to date, only 4 drugs were actually approved by regulatory agencies for the treatment of AD, which are: Tacrine (Fig. **3a**), Galantamine (Fig. **3b**), Rivastigmine (Fig. **3c**) and Donepezil (Fig. **3d**) [122].

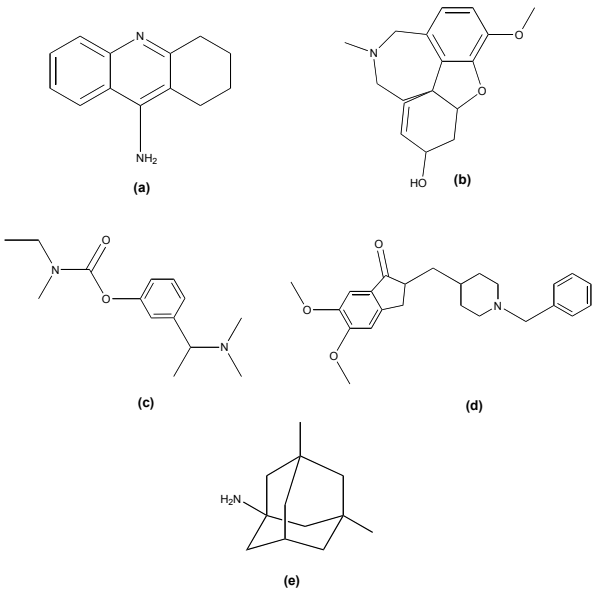

Fig. (3). FDA-approved drugs for the treatment of **(a)** tacrine, **(b)** galantamine, **(c)** rivastigmine, **(d)** donepezil, **(e)** memantine [133, 134].

Tacrine was the first drug approved for the treatment of AD. It is considered a non-competitive and non-selective reversible inhibitor to acetylcholinesterase (AChE), which has a dose-dependent efficacy, short half-life and high incidence of adverse effects and hepatotoxicity [124, 125].

Donepezil is a drug from the family of N-benzylpiperidine; it was developed, synthesized and evaluated by a Japanese pharmaceutical industry, and was approved in 1996 for its use in the treatment against AD. It is a highly selective reversible noncompetitive inhibitor of AChE, does not present serious adverse effects and significantly improves the symptoms of AD [126, 128]. However, by using the cytochrome P450 system in its metabolism, emerges the development of drug interactions with other drugs, so that their combination should be cautious [124].

Rivastigmine, a physostigmine derived-drug, is a pseudo-selective irreversible inhibitor of AChE and BChE. This drug shows good activity and tolerance in patients with AD and does not involve the cytochrome P450 system in its metabolism, reducing the possibility of occurrence of drug-drug interactions, improving cognition and generating neuroprotective effects [124, 129, 130].

Galantamine is a tertiary alkaloid extracted from various species of Amaryllidaceae, accidentally discovered in 1950. It is a selective, competitive and reversible inhibitor of AChE and contains a modulating action on nicotinic receptors and low hepatotoxicity. However, its association with other drugs requires caution since its metabolism uses the cytochrome P450 system. This drug was only approved in 2001 for the treatment of AD, but it was used over the years for various neurological disorders [124, 125, 131].

6.2. NMDA Antagonists

Memantine (l-amino-3,5-dimethyl adamantane) (Fig. **3e**) (Table **1**) was approved in May 2002 by the European Union and, in October 2003, was licensed by the FDA (Food and Drug Administration). This drug decreases excitotoxicity and neurodegeneration caused by excessive action of glutamate [134, 135].

Memantine is a noncompetitive NMDA receptor antagonist used for the treatment of AD in mild to severe stages and presents a half-life less than 60 hours. Memantine reduces excessive glutamatergic neurotransmission, may decrease hyperphosphorylation of Tau protein and protects against toxicity induced the Abeta peptide [136, 139]. The blocking property of this receptor was discovered by Kornhuber *et al.,* [140] when used as a selective inhibitor of the NMDA receptor, the MK-801 compound.

In the 90s, the blocking action of memantine was elucidated by Parsons *et al.,* [141]. Memantine *in vivo*, inhibits mitochondrial function, reduces both the cerebral blood flow and the toxic effects of the neuroinflammation, and the formation of Abeta peptide [142]. Meta-analysis studies corroborate that the drug reduces the neuropsychiatric symptoms of AD when compared with a placebo [143]. However, Fox *et al.,* [138] proved that the use of memantine does not significantly improve the symptoms of agitation in people with moderate to severe AD.

Hu *et al.,* [144] found that in primary cultures of granular neurons in the rat cerebellum, a derivative of tacrine, such as bis(propyl)cognitin (B3C) (IC_{50} = 0.45 mM) proved to be 10 times more potent than memantine (IC_{50} = 4.58 uM) to decrease the glutamate-induced excitotoxicity. The B3C is a noncompetitive

Table 1. Anti-Alzheimer agents and mechanism of action.

	Agents	Mechanism	References
1	Tacrine	Non-competitive and non-selective reversible inhibitor to acetylcholinesterase	[125, 126]
2	Donepezil	Highly selective reversible noncompetitive inhibitor of AChE	[127-129]
3	Rivastigmine	Pseudo-selective irreversible inhibitor of AChE and BChE	[125, 130, 131]
4	Galantamine	Selective, competitive and reversible inhibitor of AChE	[125, 126, 132]
5	Memantine	Non-competitive NMDA receptor antagonist	[137-140]
6	Bis(propyl)cognitin (B3C)		[146]
7	LY2811376	Block the enzymes that cleave the amyloid precursor protein (APP) Non-peptide BACE1 inhibitor	[156]
8	2,2',4'-trihydroxichalcone (TDC)	BACE1 inhibitor	
9	Ginsenoside Rg1		
10	OM99-2	Potent peptide inhibitor of leucine and alanine (BACE1 inhibitor)	[157]
11	hydroxyethylamine isosteres (HEA)	BACE1 inhibitor	[158]
12	Isophthalamide		
13	des(dimethylamino)		[159]
14	LY45013A	γ-secretase inhibitor	[153]
15	Thiazolidinones (TZD)	ATP-non-competitive inhibitor	[171]
16	Bis-indole	GSK-3β inhibitor	
17	Aniline		[173]
18	Maleimides, Kenpaullone		[174]
19	Indirubin		[175]
20	Hymenialdisin		[176]
21	SB216763 (3-[2,4-dichlorophenyl]-4-[1-methyl-1H-indol-3-yl] -1H-pyrrole-2,5-dione)	Highly selective inhibitor that possesses cell permeability and acts by competing with ATP binding site	[162, 168]
22	SB415286	Blocks the glutamate induced apoptosis	[145]
23	Lithium	Deprive potassium or inhibits the enzyme competing with magnesium ions (Mg^{2+})	[179-181]
24	Valproate sodium	Reduced the phosphorylation of the Tau protein	[184]
25	Mts-L803	Inhibits Abeta peptide accumulation and improve the cognitive function	[185]
26	Piperazinyl sulfonamide analogs	GSK-3β inhibitor	[186]
27	derivatives of 6-amino-4-(pyrimidin-4-yl)pyridone		[187]
28	2-(2-phenylmorpholin-4-yl)pyrimidin-4(3H)-ones	Decreased phosphorylation of the Tau protein	[170]
29	1,3,4-oxadiazole derivatives	Highly selective inhibitors of GSK-3β	[188-191]

(Table 1) contd….

	Agents	**Mechanism**	**References**
30	Quinolone derivatives	Inhibitory activity against GSK-3β and neuroprotective action against the injury caused by the production of Abeta peptide	[192]
31	Compounds C-7a and C-7b	Interfere with the neuronal death-induced accumulation of Abeta peptides and inhibits the phosphorylation of the Tau protein	[194]
32	Pyrimidones	GSK-3β inhibitor	[195]
33	Np-1003		[196]
34	Methylthioninium chloride (TRx0237)		
35	Indomethacin	Reduces formation of Abeta	[200]
36	Ibuprofen		
37	Curcumine	Modulate eicosanoid biosynthesis and inhibits COX-1, COX-2 and LOX	[134, 197, 201, 202]
38	Magnolol	Inhibits COX	
39	α-pinene		
40	β-pinene		
41	Carvacrol		
42	Luteolin		
43	Rosmarinic acid		
44	Resveratrol		
45	Apocynin		
46	4'-O-metylhonokiol (MH)	Inhibits the induction of amyloidogenic Inhibits the activation of astrocytes	
47	Quercetin	Antioxidant	[75]
48	Myricetin		
49	AT-1792	Act on amyloid plaques	[198]

NMDA receptor antagonist that interacts only in pathological situations as well as an AChE inhibitor and antagonist of the γ-aminobutyric acid receptor subtype A [145].

A rat model had their learning and memory functions impaired by the okadaic acid, in this model the impairment was reduced followed the administration of memantine (10 mg/kg). It was assessed by the elapsed time for the animal to find a submerged platform in the Morris water maze (latency); it was significantly decreased after first session [146].

According Winblad *et al.,* [147], memantine showed benefits for daily activities of patients with moderate to severe DA when compared to a placebo, and thus lead them to a dignified life. Patient groups (already treated with acetylcholinesterase inhibitors) that received only memantine or associated with tocopherol showed no improvement in mild to moderate AD according to Dysken *et al.,* [148].

After 2 hours of memantine administration (50 mg/kg), there was increased phosphorylation at Ser9 residue from glycogen synthase kinase-3β (GSK-3β) in the cerebral cortex of mice, thus inhibiting the enzyme activity [137, 149]. In a study by Hellweg *et al.,* [150] in 2,506 patients with moderate to severe AD, individuals treated with memantine showed a significant delay in worsening of clinical condition compared with those who received placebo.

In the latency of the two-way avoidance response, the mice treated with the drug memantine and the com-

pound FTY720 had a longer latency to enter the dark compartment and showed less time spent inside the compartment that the untreated animals. Histological analysis of hippocampal neurons, showed that the animals that received FTY720 and memantine had a significant reduction in neuronal loss induced by Abeta peptide [151].

In the study of 882 patients, who received a placebo and 868 patients were treated with memantine an improvement of 1.99 in the Neuropsychiatric Inventory scale was observed when compared with the placebo group [143].

6.3. Secretases Inhibitors

The secretase inhibitors (Table **1**) block the enzymes that cleave the amyloid precursor protein (APP), thereby preventing the formation of insoluble Abeta peptides that are responsible for the formation of senile plaques. The main enzymes participating in this pathogenic mechanism are the β-secretase (BACE1) and γ-secretase [152].

According to Sinha and Liebenburg [153], the β-secretase is an interesting therapeutic target for AD, presenting an essential role in the production of Abeta. Thus, Zhu *et al.,* [154] report that subsequent to the BACE1 identification, several researchers have sought synthesizing and testing numerous inhibitors of this enzyme with regard to their Abeta reduction properties, in an attempt to retard the progression of AD in the long term.

Zhang [155] reported the LY2811376 as the first non-peptide BACE1 inhibitor drug available for oral administration in clinical trials. However, the studies had to cease when a significant increase in toxicity of the retinal epithelial cells of the animals studied was detected, thus suggesting the need for greater care during the planning, use and safety assessment of this type of drugs.

Among the compounds used for inhibition of BACE1, there are some naturally occurring compounds used in traditional Chinese medicine, such as 2,2',4'-trihydroxichalcone (TDC) and ginsenoside Rg1 [155], and other synthetic compounds such as OM99-2 [156], hydroxyethylamine isosteres (HEA), the isophthalamide [157] and a des(dimethylamino) compound [158].

Regarding the natural origin BACE1 inhibitors, the Rg1 ginsenoside is obtained from Panax notoinseng. It has been used extensively over the years in traditional medicine for improving the memory function and presented about 80% inhibitory activity against BACE1, revealing its potential protection against the degenerative effects of Abeta. Since the DCT is a family of flavonoid chalcones extracted from the Glycyrrhiza glabra, widely used as an emollient in stomach disorders and respiratory problems. It presents anti-inflammatory, antioxidant and anti-tumor activities; while more recently it has been evaluated as a potential candidate for the treatment of AD due to a surprising inhibitory activity against BACE1, suppressing the cleavage of the amyloid precursor protein and thereby reducing the levels of toxic Abeta peptide in brain tissue [155].

The OM99-2, a hydroxyethylene-containing potent peptide inhibitor of leucine and alanine, was the first compound to act effectively on the BACE1 [156, 159], while other studies of Gosh *et al.,* [157] found that in terms of structure-activity relationship (SAR), the sizes of structures and the choice of substituents in the hydroxyethylamine moiety was crucial for the inhibitory potency of the drug against BACE1, just as some bioisosteres of isophthalamide had better inhibitory potential, with good cell inhibitory activity and considerable reduction in the production of toxic Abeta peptides, such as the GRL-7234 and GRL-8234.

In 2009, Steele *et al.,* [158] have identified the aminopyrimidine-containing molecule (HTS) as a weak inhibitor of BACE1 (IC_{50} = 317 μM), and only after several optimization experiments, by molecular and rational design modeling, the HTS originated the des(dimethylamino) chemical structure, which in terms of SAR showed an enzymatic activity superior to HTS.

In addition to the drugs mentioned above, Simers and colleagues [160] obtained good results in clinical trials of LY45013A, an inhibitor of γ-secretase, which during the phase I studies showed a dose-dependent reduction in plasma levels of Abeta without important adverse effects [152].

6.4. Glycogen Synthase Kinase Inhibitors:

The Glycogen Synthase Kinase-3 is a serine/threonine kinase protein responsible for the phosphorylation and thus inactivation of glycogen synthase, the control of glycogen metabolism, regulation of cell proliferation and cell cycle. There are two isoforms of GSK-3, GSK-3α and GSK-3β. The first presents the α-aminoacid glycine in its N-terminal end, whereas the second consists of two splice variants, in which the shorter form (GSK-3β 1) is in several organs and the longer form (GSK-3β2) is present in the central nervous system [161-164].

GKS-3β activity is negatively regulated by phosphorylation of serine 9 (Ser9) and positively by phosphorylation of tyrosine 216 (Tyr216), *i.e.,* the phosphorylation of Ser9 residue reduces the activity of this enzyme, whereas the phosphorylation of Tyr216 residue promotes activation [165-167].

The activation of GSK-3β causes the hyperphosphorylation of Tau protein which induces depolymerization of microtubules, leading to the formation of neurofibrillary tangles and destabilization of the neuronal processes. Microtubules are cytoskeletal components that are involved in the maintenance of neuronal morphology and axon and dendrite formation processes [168, 169].

Thiazolidinones (TZD) were the first ATP-noncompetitive inhibitors (Table **1**) with a potential to originate drugs for the treatment of AD [170]. However, other compounds such as bis-indole [171], aniline [172], maleimides, kenpaullone [173] indirubin [174] and hymenialdisin [175] have been described as inhibitors of GSK-3β.

The study by Hu *et al.,* [161] corroborated the hypothesis that hyperphosphorylation of the GKS-3 is involved in the neurodegeneration-induced Abeta peptide. In this study, SB216763 (3-[2,4-dichlorophenyl]-4-[1-methyl-1H-indol-3-yl] -1H-pyrrole-2,5-dione) inhibits the GSK-3 enzyme. The SB216763 is a highly selective inhibitor that possesses cell permeability and acts by competing with ATP binding site. The destabilization of microtubules induced by rotenone, a toxin that inhibits the mitochondrial complex I, was attenuated by using the GSK-3β inhibitor SB216763 in human neuroblastoma cells SH-SY5Y [167]. According to Wang *et al.,* [176], the SB216763 is a potent imaging agent that can be used in positron emission tomography (PET) of GSK-3.

To determine the relationship *via* PI3-K/Akt/GSK-3β with the NMDA receptor signaling pathway in glutamate-induced excitotoxicity, the SB415286 inhibitor was used (pre-treatment) in primary cultures of cerebellar granular neurons in rats and it was observed that this compound blocks the glutamate induced apoptosis [144]. Moreover, mice pretreated with inhibitors SB216763 (0.6 mg/kg) and SB415286 (1 mg/kg) for 3 days before intracranial radiation of a single dose of 7 grays (Gy), improved their performance in the Morris water maze platform [177].

Lithium was the first inhibitor of GSK-3 discovered and presents two possible mechanisms of action: it may cause deprivation of potassium or inhibit the enzyme competing with magnesium ions (Mg^{2+}). Lithium, besides reducing hyperphosphorylation of the Tau protein, is capable of reducing the production of Abeta peptide [178-180]. Noble *et al.,* [181] observed a significant reduction in GSK-3 activity and Tau protein phosphorylation after administering intraperitoneally lithium for 30 days in transgenic mice that overexpress the Tau human protein.

Lithium and valproate are inhibitors of the enzyme GSK-3β, and reduced the phosphorylation of the Tau protein in animal models, according to Tariot and Aisen [182]. However, divalproex sodium has accelerated the loss of brain volume after one year of treatment, in addition to a greater cognitive impairment according to Fleisher *et al.,* [183].

In transgenic mice treated with a peptide inhibitor of GSK-3, the mts-L803, it was observed the inhibition of Abeta peptide accumulation and improvement in cognitive function [184]. According to Berg *et al.,* [185], piperazinyl sulfonamide analogs inhibit GSK-3β, besides having good solubility and permeability through the blood brain barrier and Caco-2 assays.

In a study by Coffman *et al.,* [186], derivatives of 6-amino-4-(pyrimidin-4-yl)pyridone showed inhibitory activity against the GSK-3β enzyme in a cellular enzyme inhibition assay. Also, the 2-(2-phenylmorpholin-4-yl)pyrimidin-4(3H)-ones decreased phosphorylation of the Tau protein in mice when administered orally, by inhibiting GSK-3β [169].

The 1,3,4-oxadiazole derivatives are potent and highly selective inhibitors of GSK-3β, three of these compounds (2-methyl-5-{3-[4-(methylsulfonyl)-, 2-methyl-5-{3-[4-(methylsulfinyl)-, and 2-methyl-5-{3-[4-(methylsulfonyl)-(3)-phenyl]-1-benzofuran-5-yl}-1,3,4-oxadiazoles (MMBO), IC_{50} = 66, 35 and 42 nM, respectively) showed good pharmacokinetic profiles and high absorptions by the blood brain barrier. The MMBO showed high selectivity for GSK-3 in inhibiting the phosphorylation of the Tau protein in cultured primary neural cells and normal rat brain, showing to be a good drug candidate for the treatment of AD [187-190].

Two quinolone derivatives (IC_{50} = 35 and 158 nM) had inhibitory activity against GSK-3β and neuroprotective action against the injury caused by the production of Abeta peptide in MC65 cells [191]. The prolyl isomerase Pin1, an enzyme that controls the phosphorylation of proteins, inhibits GSK-3β activity and decreased the PPA levels, which demonstrates a new protection mechanism against AD [192].

Compounds C-7a and C-7b (120-130 nM) were able to interfere with the neuronal death-induced accumulation of Abeta peptides and to inhibit the phosphorylation of the Tau protein (pThr231, pSer396, pThr181 and pSer202) *in vitro*. Furthermore, *in vivo*, 50 mg/kg of C-7a decreased the phosphorylation of the Tau protein (Ser202) in the hippocampus of the brains of mice. The C-7a may be considered a disease-modifying agent and a potent candidate for the treatment of AD [193].

According Uehara *et al.,* [194] pyrimidones showed inhibitory activity against GSK-3β and good permeability in mouse brains and reduction of the phosphorylation of the Tau protein. According Giacobini and Gold [195] some GSK-3β inhibitors are in clinical phase trials, such as Np-1003, developed by the Noscira S.A., SAN-161 (Sanoimmune) and an inhibitor of the aggregation of the Tau protein, methylthioninium chloride (TRx0237) studied at the University of Aberdeen and TauRx Therapeutics.

6.5. Complementary Treatments Applied to AD

Regarding the pharmacological treatment of AD, several authors state that, in addition to therapies already described in this article, there are other approaches that can collaborate in the process of stabilization of the disease, such as the use of anti-inflammatory, antioxidant, estrogenic replacement and vaccine, among others [196-198].

The anti-inflammatory drugs (Table **1**) act by reducing the inflammatory response in the brain tissue, as in the studies conducted by Lim *et al.,* (2001) [199], which suggested that indomethacin and ibuprofen would be able to reduce Abeta formation. However, prolonged use can cause many unwanted side effects such as kidney and stomach problems [200]. Other examples of anti-inflammatory drugs are: curcumin, capable of modulating eicosanoid biosynthesis and inhibiting COX-1, COX-2 and LOX; Ginkgolide B, which is an antagonist of platelet activating factor; magnolol; A-pinene; Beta-pinene; carvacrol; luteolin; Rosmarinic acid; resveratrol; and apocynin, which also act as inhibitors of COX. Furthermore, the compound 4'-O-methylhonokiol (MH) has demonstrated an important inhibitory capacity on the induction of amyloidogenesis through anti-inflammatory mechanisms. It inhibits the activation of astrocytes in brain tissue and several other signaling cascades related to inflammation and oxidative stress. Thus, all these activities favor the inhibition of the inflammatory processes associated with the physiology of AD and reduce the deleterious consequences of this disease [133, 196, 200, 201].

Antioxidants prevent free radical formation, reducing oxidative stress on the cells and thus assisting in the treatment of AD, exerting a probable neuroprotective effect. The vitamin E demonstrated benefits on AD, slowing the natural course of the disease [133]. Other examples of antioxidants are resveratrol, apocynin [196], and some flavonoids such as quercetin and myricetin, which through their known antioxidant activity prevent the inactivation of acetylcholine receptors [74]. Similarly, the estrogen-replacement therapy also acts through neuroprotective mechanisms in the prevention of AD. Estrogens exert effects on various receptors of the neuronal surface, promoting the release of neurotransmitters and increasing the cerebral blood flow. In addition, there are cases of estrogen reducing the neurotoxicity promoted by Abeta [165]. Regarding the anti-Alzheimer vaccine AT-1792, it was developed to act on amyloid plaques but showed significant adverse effects leading to a discontinuation of its use [176].

CONCLUSION

The multifactorial character of AD's pathogenic mechanism hinders the development of fully effective drugs for its therapy. Thus, several researchers continue in the search for new drug candidates for the treatment of AD. Nevertheless, all the drugs available so far act only on the symptoms, which mean that these treatments are often found to be unsatisfactory in view of a permanent stabilization of the disease after the diagnosis. In addition, maintenance of the treatment from the patient himself or caregiver is often difficult, since this type of disease often requires drug combinations to achieve better clinical outcomes. It is in this aspect that the early diagnosis facilitates the maintenance of the memory and cognitive functions of these patients. The use of various drugs and drug candidates discussed in this article may help to improve the prospects of the anti-Alzheimer's therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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