Pharmacological Treatment of Alzheimer's Disease

Scientific and Clinical Aspects

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To all those who helped me be a better person and understand the importance of life:

They brought me to this world and taught me how to live – my mother, Belmira, and my father, João.

My small but immensely strong and true circle of friends, for words of encouragement.

My lifelong teachers, for their positive influence.

The reason for my existence, Gabriela.

The one who completes me, inspires me, brings me energy, and always accompanies me, my wife Cláudia.

Preface

The damage caused by Alzheimer's disease is quite cruel, and among all the damages manifested, without a doubt, memory impairment is the most relevant, as it takes away the best moments, the memories, what helps us keep alive and with hope. Although recognized in 1906, it took a long time for science to effectively achieve advances in the pathophysiology, diagnosis, and treatment of Alzheimer's disease.

As it is a neurodegenerative disease, Alzheimer's affects cognition and behavior, and the mechanisms involved include a vast network of neurotransmitters, proteins, and enzymes, resulting in highly complex morphological, anatomical, and molecular manifestations.

The pharmacological treatment of Alzheimer's disease, so far, although it does not bring a cure, if applied in a timely manner, can delay the progress of the disease and provide better quality of life for patients with a confirmed diagnosis. People with Alzheimer's can live for more than 10 to 12 years after beginning treatment, and it is vital to choose the correct medications and adopt pharmacotherapy with full adherence by family members, caregivers, and the patient.

This book is the result of work I started in 2007 with patients with some type of dementia in a long-stay institution for the elderly. As a pharmacist, I work on the development of protocols and do pharmacotherapeutic monitoring of patients with Alzheimer's disease. During this same period, also as a researcher, my work is focused on the early diagnosis of Alzheimer's through biomarkers. Precisely early diagnosis should be the key to more effective pharmacological treatments, perhaps during the prodromal period, avoiding the accumulation of beta amyloid protein and the formation of neurofibrillary tangles characterized by the TAU protein.

The chapters were written by renowned researchers, physicians, biologists, biodoctors, pharmacists, and other health professionals, all with extensive experience and expertise in the subject, providing information of great relevance and importance for those who work with Alzheimer patients and the general public.

We hope to be able to contribute to the strengthening of science, the basis of knowledge! Science can take us to incredible places; without science, there is no evolution.

Ribeirão Preto, SP, Brazil Gustavo Alves Andrade dos Santos

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The opportunity and privilege of writing a book is always unique and memorable and is part of a trajectory, in my case, started a few decades ago. There were many words of support and encouragement coming from family, friends, colleagues, research participants, and the institutions with which I maintained or maintain a working relationship.

Thank you all for your encouragement, motivation, and partnership.

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Chapter 1
Introduction

Gustavo Alves Andrade dos Santos

1.1 The Origin of the Alzheimer's Disease and Advances in Pharmacology

AD was first presented by the German psychiatrist and neuro pathologist Alois Alzheimer in November 1906 at the 37th Meeting of Psychiatrists in Southeast Germany, giving rise to one of the most important medical discoveries in the modern world. Alzheimer described this case as "A disease peculiar to neurons in the cerebral cortex," identified in the patient Auguste D., 50, who, according to the medical record, started to present cognitive deficits, memory loss, and confusion about time and space, with progressive worsening, leading to death 5 years later. Alois Alzheimer identified necropsy in the patient's brain tissue, with the presence of distinct plaques and neurofibrillary tangles [1, 2].

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A few decades later, still in the twentieth century, science managed to relate Alois Alzheimer's findings with senile plaques and neurofibrillary tangles, that is, the macroscopic "postmortem" cortical observations from the beginning of the century, and made a lot of sense to understand a disease hitherto unknown to the scientific community. Advances in the identification and recognition of Alzheimer's disease strengthened the foundations of neuroscience at the end of the twentieth century.

In the early twentieth century, between 1906 and 1910, another German psychiatrist, Emil Kraepelin, called the new pathology Alzheimer's disease (AD) a just homage to Alois Alzheimer. The term started to be used for cases of this type of dementia, a condition that can also affect presenile patients, that is, before the age of 65 [3].

Estimates predict, for the United States of America, that in 2050, there will be 13.8 million patients with AD aged 65 years or more, representing a significant increase compared to the current 5.8 million [4]. In Brazil, it is estimated at 7.7 Alzheimer patients for every 1000 people per year in individuals over 65 years of age. Every five, this rate practically doubles, with a higher incidence found among women, especially when they are older [5].

The impact of Alzheimer's disease on the economy is great, with world cost estimate in 818 billion dollars, and being foreseen an increase in this number to 1 trillion dollars until 2018 with its prevalence and incidence, showing an increase of 35% compared to 2010, according to estimates of World Alzheimer Report Updates 2015. This cost is even below market values (billing) from companies like Apple (742 billion of dollars) and the Google (368 billion of dollars). The number of people living with dementia doubles in severity in 20 years, rising to 74.7 million in 2030 and 131.5 million in 2050 [6].

There are two proteins involved in the pathophysiology of Alzheimer's disease: tau and beta-amyloid. Their respective fragments come together, giving rise to neurofibrillary tangles and senile plaques, respectively. They accumulate in the cerebral cortex, with projections to the hippocampus, a region where memory is stored (thus compromising its formation) and then expand through other areas of the brain, impairing the senses. The multiple stages of the disease are characterized by the progression and expansion of these plaques. Currently, the treatments used for Alzheimer's disease aim to improve the quality of life of patients, being more effective when used dearly, so the new studies consist of vaccines and monoclonal antibodies to prevent the aggregation of these proteins [7, 8].

The imbalance between kinases and phosphatases contributes substantially to the aggregation of the tau protein. Posttranslational changes canal so contributes to this phenomenon. In addition, oxidative stress, cleavage, glycation, nitration, and polyamidation canal so contribute to the formation of neurofibrillary plaques. The main neurotransmitter revolved in this process is acetylcholine (ACh), and its deficiency supports the cholinergic hypothesis. The purpose of inhibiting the activities of acetylcholinesterase (AChE), an enzyme responsible for the cleavage of ACh in the synaptic cleft, is justified, promoting an increase in the levels of this neurotransmitter. Alzheimer's disease can evolve in three symptomatic ways: It starts with

memory lapses, and then the patient may experience hallucinations and violent behavior and, finally, total dependence on family members, becoming unable to perform essential activities if eating and get dressed [9, 10].

Apolipoprotein E (ApoE) is responsible for repairing damage to neurons, in addition to one of the main proteins in human plasma. It is also involved in the absorption, transport, and redistribution of triglycerides and cholesterol through tissues. ApoE is present in brain amyloid plaques, promoting fibrinogenesis of the b-amyloid peptide and binding to the tau protein, decreasing its phosphorylation. There are some variables and/or mutations in the E4 gene (found on chromosome 21) that encode this protein correlating cholesterol with AD. Patients with this dementia have significant elevated levels of the ApoE gene, increasing the affinity of this protein and beta-amyloid, thus facilitating its deposit and accumulation. The presence of the two alleles of this type of variation can decrease the onset of the disease [11].

1.1.1 Pharmacological Treatment: Therapy Through the Use of Medications

Claudio Galeno, considered the official surgeon of gladiators, lived between 131 and 201 AD, being recognized as the first to reflect on the importance of pharmacology and its theoretical basis. His is the phrase, "The empiricists claim that everything is discovered through experience. However, we maintain that discovery occurs partly through experience and partly through theory. Neither experience not theory alone is able to discover everything." Philippus Aureolus Theophrastus Bombastus von Hohenheim, known as Paracelsus, professor at Basel University, believed that medicine and pharmacy should be based on physical and chemical laws, being considered the precursor of modern pharmacology. In the work *Paramirum*, he highlighted the clinical observation of the patient, in addition to proposing the axiom that has become famous in pharmacology [12]:

> If you want to adequately explain what a poison is, what then is not a poison? All things are poison, and nothing is without poison; only the dosage establishes whether something is not a poison.

It was only in 1847 that Rudolf Buchheim founded the first Institute of Pharmacology at the University of Dorpart in Estonia, making pharmacology a subject of study in science, that is, pharmacology became the object of science [12]. Oswald Schmiedeberg, considered the "Father of Pharmacology," developed extensive chemical and pharmacological studies and trained most of the physicians who were professors of pharmacology [13, 14]. One of his students John Jacob Abel was the founder of the first chair of pharmacology in the United States of America, in Michigan, in 1890. It was precisely in the United States that basic laboratory-developed sciences became part of medical training [15].

Paul Ehrlich, in 1900, brought the concept of receptor, which had the objective of defining locations on the cell surface with specific molecular characteristics, where substances interact in a punctual way, connecting at this point as a keylock system. Ehrlich was also blamed for the introduction of therapeutic pharmacology, which, very different from the experimental pharmacology of the early nineteenth century that tested drugs in healthy animal models or tissues, started to cause disease in animal models to test drugs and medicines [15, 16].

Pharmacology consists of two areas of interest, pharmacokinetics and pharmacodynamics. In pharmacodynamics, the most important issue is the dose-response relationship, which describes the dependence of a drug's effect on its concentration on its receptor. In the field of pharmacokinetics, the main topics are the distribution of drugs in the various compartments of the body and the course over time of their concentration in the blood [17].

In 1928, when penicillin was accidentally discovered by the British pharmacologist Alexander Fleming, the dimension of this new science recognized as pharmacology did not yet exist. When penicillin was discovered in 1928, even if accidentally, the 1st pharmacological revolution began there [18–20].

A few years later, in 1940, Howard Florey and Ernst Chain improved experiments with antibiotics, allowing their large-scale production [19, 20]. In the mid-twentieth century, there was an expansion with advances in the development of vitamins, sulfonamides, hormones, psychotropics, antihistamines, and various vaccines. New therapeutic classes were created and recognized, infant deaths were reduced by half, while maternal deaths due to childbirth had to over 90%. Some diseases such as tuberculosis, diphtheria, and pneumonia could be treated and healed for the first time in human history. This period became known as the "Golden Age of the Pharmaceutical Industry" [20, 21].

Currently, drugs of synthetic origin have become the largest portion of the pharmaceutical market, bringing positive results, for example, the improvement of research methods, with increased therapeutic efficacy of drugs, making them safer and reducing their toxicity [20]. We have arrived at the era of the "3rd Pharmacological Revolution"! [20] The pharmaceutical industry is going through a period of great expansion, with the launch of new molecules, resulting in the possibility of treatment for diseases such as Alzheimer's, cancer, AIDS, multiple sclerosis, malaria, and diabetes, among others [22, 23].

1.1.2 Advances in the Treatment of Alzheimer's Disease

The various treatment hypotheses for Alzheimer's disease drive clinical drug trials in various research centers, pharmaceutical laboratories, and universities around the world.

A few decades ago, in 1976, the cholinergic theory, proposed by Peter Davies and A.J.F. Maloney [24], was that acetylcholine deficit could be the probable cause involved in the pathophysiological process of AD. They evaluated and compared the

activities of "key" enzymes involved in the synthesis of neurotransmitters, including acetylcholine (ACh), gamma-aminobutyric acid (GABA), dopamine, noradrenaline, and serotonin (5-HT), in 20 brain regions of patients with AD and control group. Choline acetyltransferase (ChAT) activity in the brains of people with AD was greatly reduced in the hippocampus, amygdala, and cortex, while the concentration of ACh was reduced in the synapses [25–27]. The ChAT enzyme plays a key role in the synthesis of Ach, and its catalytic activity requires the substrates: choline, acetyl-CoA, and adenosine triphosphate (ATP). Failure to concentrate ACh, therefore, was the first idea postulated as an explanation for Alzheimer's pathophysiology [24, 28].

Drugs capable of inhibiting acetylcholinesterase (IAChE) canal levitate cognitive impairment in AD patients by inhibiting ACh degradation. Esterase inhibitors have been used for more than 20 years since the US FDA approved the use of tacrine, a drug withdrawn from use due to its hepatotoxicity. Then came the drugs called the 2nd generation of IAChE: donepezil, rivastigmine, and galantamine. In patients with mild and moderate AD, these drugs can improve cognitive status, in addition to having fewer side effects compared to tacrine. The latest meta-analysis carried out with these drugs has shown that the clinical effects are modest in the treatment of AD although a clear improvement in the quality of life of these patients has been verified. In addition, IAChE fail to prevent the spread of Alzheimer's disease [29, 30].

In 2011, Santos et al. [31] demonstrated that rivastigmine tartrate (Fig. 1.1) can bring very interesting results in the reduction of another type of esterase, butyrylcholinesterase (BUChE). In this study, researchers compared serum levels of AChE and BUChE in oral to transdermal forms in patients with AD, correlating the findings with Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) results. The MMSE was evaluated in two moments: beginning (day zero) and end, 180 days later, as shown in Table 1.1, the same for the NPI (Table 1.2). And finally, in the assessment of BUChE levels, one of the two esterases involved, hypothetically, with the evolution of Alzheimer's disease, it was found a decrease in its levels in two measurement moments (Table 1.3).

In 1992, Mattson et al. described the hypothesis of calcium homeostasis as one of the causes of the evolutionary process of Alzheimer's disease. The studies carried out by these researchers concluded that the amyloid beta (Aβ) protein can raise intracellular calcium levels and make neurons more vulnerable to environmental stimuli [33]. Khachaturian, some time ago, was the first to suggest this proposal [34], and since then, there have been many efforts to clarify this hypothesis. A plasma protein called calcineurin may be responsible for triggering an inflammatory

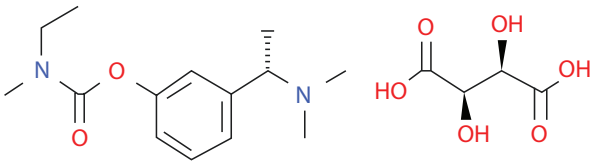

Fig. 1.1 Rivastigmine tartrate. (Source: Chemspider, 2021 [32])

Table 1.1 MMSE assessment for oral and transdermal rivastigmine (patch) [31]

	Day zero	Day 180
Rivastigmine oral	19.4 (±4.1)	14.1 (±7.0)
Patch (patch)	20.2 (±7.0)	16.2 (±6.8)

Source: Author himself

Table 1.2 NPI assessment for oral and transdermal rivastigmine (patch) [31]

	Day zero	Day 180
Rivastigmine oral	33.4 (±11.2)	27.1 (±12.3)
Patch (patch)	40.4 (±20.2)	29.3 (±18.0)

Source: Author himself

Table 1.3 Evolution of BUChE levels in patients using rivastigmine [31]

	Day zero	Day 90	Day 180
Rivastigmine oral	4179.5 (±1799.2)	3782.9 (±1798.1)	5544.6 (±2109.5)
Patch (patch)	6618.2 (±2095.6)	6165.5 (±2095.5)	6339.4 (±2451.1)

Source: Author himself

Table 1.4 Current and available treatments for Alzheimer's disease [11, 31, 40–42]

Drug	Memantine	Rivastigmine	Donepezil	Galantamine
Elimination half-life	60–100 hours	1–2 hours	7 hours	70 hours
Available in the year (FDA)	2003	1998	1997	2000
Chemical class	Aliphatic amine	Carbamate	Piperidine	Phenanthrene alkaloid
Biotransformation	Liver (CYP450)	Synaptic metabolism	Liver (CYP2D6, CYP3A4)	Liver (CYP2D6, CYP3A4)

Abbreviations: *FDA* Food Drug Administration; *CYP* cytochrome p450 isoenzyme
Source: Author himself

process in astrocytes, which are upregulated in animal models. In addition, calcium homeostasis is directly related to learning and memory processes [35].

Memantine, a noncompetitive brain glutamate receptor antagonist drug, was approved in Europe in 2002 and in the United States in 2003 [36, 37]. It is not an IAChE. It works by blocking the current flow of calcium through the N-methyl D-aspartate (NMDA) receptors, reducing the excited toxic effects of glutamate [38]. Memantine also antagonizes 5-HT3 (type 3 serotonergic receptors) and nicotinic-type cholinergic receptors. Inhibition of NMDA receptors can also reduce alpha secretase inhibition and thus inhibit Aβ production [39].

In summary, when it comes to current treatments for Alzheimer's disease, the drugs used are based on inhibiting esterases: AChE and BUChE or antagonizing NMDA receptors (Table 1.4).

In 2019, clinical trials for the development of drugs for the treatment of Alzheimer's disease were mostly based on the hypothesis of the formation of senile plaques by the degradation of the Aβ protein (Table 1.5).

Table 1.5 Percentage of clinical trials for Alzheimer's disease in 2019

Hypothesis	%
Amyloid hypothesis	22,3
Neurotransmitters hypothesis	19,0
Tau propagation hypothesis	12,2
Mitochondrial cascade and related hypothesis	17,0
Neurovascular hypothesis	7,9
Exercise hypothesis	6,6
Inflammatory hypothesis	4,6
Diabetes hypothesis	2,3
Virus hypothesis	0,5
Other	8,4

Source: Adapted from Liu et al. [43]

The Aβ protein was isolated by Glenner and Wong in 1984 and brought the possibility of improving diagnostic and therapeutic models related to the emergence and detection of Alzheimer's disease [44]. Aβ is a peptide composed of 39–43 residues derived from multiple proteolytic cleavages of APP (amyloid precursor protein) [45, 46]. The amyloid beta protein (A beta) is believed to be a key molecule in the pathogenesis of Alzheimer's disease (AD) as it has a tendency to aggregate. Its neurotoxicity combined with genetic linkage studies led to the hypothesis of AD pathogenesis [47].

High concentrations of Aβ protein are neurotoxic to neuronal maturation as they cause atrophy of dendrites and axons, followed by neuron death [48].

Current treatment strategies based on the Aβ protein hypothesis are divided into two categories [49, 50]:

- B-secretase inhibitors
- γ-secretase inhibitors

Monoclonal antibodies occupy a prominent position as molecules capable of delaying the advance of Alzheimer's disease or even slowing its evolution. Drugs such as solanezumab, gantenerumab, aducanumab, and crenezumab have been evaluated for these properties [49–53]. The most intriguing question for science regarding the effects of these drugs is undoubtedly, When early treatment should be started?

Solanezumab is an anti-Aβ immunotherapy treatment; it is a monoclonal antibody (mAb) that recognizes a linear epitope in the middle domain of the Aβ peptide, preferentially binding to soluble amyloid [54]. In humans, that is, in studies carried out with volunteers, solanezumab has been observed to increase plasma and cerebrospinal fluid (CSF) levels of Aβ peptides (1–40) and (1–42), which has led to speculation that solanezumab may be mobilizing amyloid plaques in the central nervous system (CNS) [55].

Unfortunately, in phase III clinical trials, solanezumab has been shown to be ineffective in individuals with Alzheimer's disease at mild-to-moderate stages, with no effect on brain Aβ concentration [56, 57]. One possibility to explain these results

regarding the amyloid hypothesis is that Aβ is necessary but not sufficient to cause Alzheimer's disease [58]. The Expedition Pro trial was created to investigate the effects of solanezumab on the prodromal stage of Alzheimer's disease, a stage where memory is already deteriorating but at cost due to insufficient scientific evidence for the expected benefits [59].

Gantenerumab is also a monoclonal antibody capable of binding to oligomeric and fibrillar Aβ and capable of activating microglia-mediated phagocytic plaque clearance, but unfortunately like solanezumab, it failed in phase III clinical research [60]. Crenezumab has also had two phase III trials in AD patients closed. This occurred on January 30, 2019. The drug in question, a monoclonal antibody, can bind to various Aβ, including monomers, fibrils, and oligomers. Aducanumab is a monoclonal antibody that targets aggregated forms of Aβ; however, although it can significantly reduce Aβ deposition, its clinical trials were halted in March 2021 [43]. But in June 2021, the FDA approved the use of aducanumab through the Accelerated Approval Route, an approval mechanism specific to a serious or life-threatening disease that may have therapeutic benefit. Aducanumab is the first therapy for Alzheimer's since 2003, being also the first directly indicated for the pathophysiology of the disease, that is, the presence of amyloid plaques in the brain. Clinical trials with aducanumab have shown that a reduction in these plaques can lead to a reduction in the clinical decline of this dementia [61].

Another drug, verubecestat (MK-8931), reduced CSF Aβ levels by up to 90%; however, there was no improvement in cognitive decline in people with AD, in addition to the presence of side effects [62]. The compound AZD3293 or lanabecestat is a BACE1 inhibitor that can reduce Aβ concentrations in CSF by up to 75%; however, on June 12, 2018, phase II/III studies were discontinued due to lack of drug efficacy. Atabecestat (JNJ-54861911), BACE1 inhibitor, induced a robust 95% reduction in Aβ levels in phase I trials, but the manufacturer discontinued this program in May 2018. Umibecestat had its clinical research studies discontinued in phase II/III as the results pointed to a worsening of the cognitive condition. Elenbecestat (E2609) is in phase III of clinical research, and it is also a BACE1 inhibitor and can reduce Aβ levels in the CSF by 80% [43, 63, 64].

The tau protein hypothesis, formulated as a possible cause of Alzheimer's disease, proposes excessive or abnormal phosphorylation of tau as responsible for the transformation of normal adult tau into PHF-tau (paired helical filament) and neurofibrillary tangles (NFTs). Tau is a highly soluble microtubule-associated protein (MAP). Tau protein interacts with tubulin to stabilize microtubule assembly through its isoforms and phosphorylation [65].

Tau is a family consisting of six isoforms with a range of 352–441 amino acids. The longest tau isoform in the CNS has four repeats (R1, R2, R3, and R4) and two insertions (441 amino acids in total). The shortest isoform has three repeats (R1, R3, and R4) and no insertions (352 total acidic amino acids). The six tau protein isoforms are present in an often hyperphosphorylated state in paired helical filaments of AD [65].

Hyperphosphorylation occurs by mutations that alter the function and expression of tau isoform. How tau aggregates in the absence of mutations is not known, but it

will likely result in increased phosphorylation, protease action, or exposure to polyanions such as glycosaminoglycans [66]. Hyperphosphorylated tau destroys microtubules and sequesters normal tau, MAP 1 (microtubule-associated protein 1), MAP 2, and ubiquitin in tangles of PHFs. This insoluble form damages cytoplasmic functions and interferes with axonal transport, which can lead to cell death [67].

In addition to the strategies mentioned above, there are other molecules understudy for the treatment of Alzheimer's disease. Table 1.6 shows the main compounds and the respective stages of clinical research at this time.

Table 1.6 Current status of drugs in clinical research for Alzheimer's disease [43, 68–71]

Drug	Mechanism of action (MOA)	Phase	NCT number
AAB-003 (PF-05236812)	Aβ-specific mAb	Phase I (finished)	NCT01193608
AAB-003 (PF-05236812)	Aβ-specific mAb	Phase I (finished)	NCT01193608
AADvac1	Tau vaccine	Phase II	NCT02579252
ACI-24	Aβ vaccine	Phase I	NCT02738450
ACI-35	Tau vaccine	Phase I	ISRCTN13033912
Aducanumab (BIIB037)	Aβ-specific mAb	Launched, approved by FDA	NCT02484547
ALZT-OPT1	Interferes with the inflammatory process	Phase I/II	NCT04570644
Atabecestat (JNJ-54861911)	BACE1 inhibitor	Phase III (finished)	NCT02569398
CAD106	Aβ vaccine	Phase II	NCT01097096
Cambinol	Inhibition of nSMase2 enzyme, blocks tau spread	Phase I	Unidentified
Celecoxib	Nonsteroidal anti-inflammatory drug (NSAID)	Phase III (finished)	NCT00007189
Crenezumab	Aβ-specific mAb	Phase III (finished)	NCT02670083
CSP-1103	Cytokine reduction/removal of tau and AB42; nonsteroidal anti-inflammatory drug (NSAID)	Phase III	Unidentified
Donanemab (N3pG-Aβ)	Aβ-specific mAb	Phase II	NCT03367403
Elenbecestat (E2609)	BACE1 inhibitor	Phase III	NCT02036280
Gantenerumab	Aβ-specific mAb	Phase III	NCT03443973
Gemfibrozil	Micro RNA-107 expression regulator	Phase I	NCT02045056
GV-971	Sodium oligomannate	Phase III	NCT02293915
Intepirdine SB-742457, RVT-101	Antagonist of the serotonin receptor 6 (5-HT)6	Phase III (finished)	NCT02586909

(continued)

Table 1.6 (continued)

Drug	Mechanism of action (MOA)	Phase	NCT number
Ketasyn (AC-1202)	Supplement dietary	Phase IV	NCT01122329
Lanabecestat (AZD3293)	BACE1 inhibitor	Phase III (finished)	NCT02783573
Lecanemab (BAN-2401)	Degradation of AB_{42}	Phase III	NCT03887455
LMTM (TRx0237)	Tau aggregation inhibitor	Phase III	NCT01626378
MEDI1814	Aβ-specific mAb	Phase I	NCT02036645
MK-8931 Verubecestat	BACE1 inhibitor	Phase III (finished)	NCT01953601
Naproxen	Nonsteroidal anti-inflammatory drug (NSAID)	Phase III (finished)	NCT00007189
Neflamapimod (VX-745)	p38a kinase inhibitor	Phase II	NCT02423122
Rosiglitazone	Type II diabetes drug	Phase III (finished)	NCT00490568
Simvastatin	Inhibition of HMG-CoA reductase cholesterol-lowering drug	Phase IV	NCT00842920
Solanezumab (LY2062430)	Aβ-specific mAb	Phase III	NCT02760602
Umibecestat (CNP520)	BACE1 inhibitor	Phase II/III (finished)	NCT03131453
Valaciclovir	Antiviral drug	Phase II	NCT03282916

NCT number – (https://clinicaltrials.gov)
Source: Adapted from Liu et al. [43]

Other molecules are noteworthy, such as resveratrol and curcumin, both with actions related to reducing oxidative stress and preventing the formation of free radicals, trying to maintain the integrity of the neuronal membrane [72]. Curcumin and resveratrol have presented important pharmacological activities, with anti-inflammatory actions and antimicrobials, among others, as well as activities against various degenerative diseases including neuronal protection and under circumstances that may be present in the development of AD [73].

Resveratrol has cardioprotective and anti-inflammatory effects, in addition to protection against oxidation and toxicity, preventing the process of apoptosis of neurons, also proposing to be neuroprotective in degenerative diseases, mainly in Alzheimer's disease [74].

Curcumin is known for its chemical structure (C21H20O6) which consists of two aryl rings containing attached OH groups. It is a compound low molecular weight polyphenol (368.37 g/mol) with possibility of having neuroprotective properties, being able to protect against apoptosis [74].

Curcumin and resveratrol demonstrated as antioxidant and anti-inflammatory and in the decrease of β-amyloid aggregates in the central nervous system. Even if the effectiveness of curcumin and resveratrol is not proven as the future molecule for the production of new drugs, their search has shown that there is a possibility of use of these substances due to their neuroprotective characteristics [72].

The pharmacological treatment of Alzheimer's disease strongly depends on the recognition of the entire pathophysiological process involved in the onset and progress of this disease. There are several hypotheses understudy, some already discarded and others in full confirmation phase. The entire neurodegenerative process seems to be triggered by a trigger of reactions that involve neurotransmitters, proteins, and other molecules, some of which were previously unknown. Factors such as lifestyle, age, and comorbidities, in addition to genetic aspects, may make some sense as long as there is a correlation with the disease.

We have never been so close to unraveling the puzzle called Alzheimer's disease, and every effort has been made in this direction. Honestly, I don't believe in a "miracle molecule" or in any kind of 100% effective healing process, but I believe that the key to solving the cure for Alzheimer lies in containing the evolution of the disease still in the prodromal phase because later, with the plates and tangles formed, becomes more difficult, almost impossible to reverse the process.

Pharmaceutical corporations around the world are fighting against time and are focusing on a true "Gold Rush" to unravel this mystery, the ultimate cure for Alzheimer's disease. Who knows, soon the good news will start to arrive; in the meantime, it is important to recognize the treatments available, either to slow down progression or to mitigate behavioral changes [75].

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Chapter 2
Principles of Pharmacology in Dementia

Francisco Assis Carvalho Vale, Judith Thomas Tayra, and Carina Tellaroli Spedo

2.1 Introduction

Alzheimer's disease (AD) is a neurological pathology of degenerative nature, which causes neuronal death and brain atrophy of unknown cause, and is clinically manifested by progressive cognitive losses and behavioral changes that inexorably progress to dementia and death. AD is the leading cause of dementia worldwide and characteristically affects the elderly population although it can occur much less often in people under 60 years old. About 95% of cases occur in people 65 years of age and older.

The disease is named after the German psychiatrist Alois Alzheimer, who first described it. Alzheimer followed a 51-year-old patient, called Auguste D, with a progressive picture that began almost 5 years earlier with memory loss, language difficulty, apraxia, behavioral changes, delusions, and hallucinations.

The patient died at the age of 56, and Alzheimer himself examined her brain postmortem. He found, in addition to intense brain atrophy, the presence of neurofibrillary tangles and senile plaques. He presented the case at a meeting of psychiatrists in Germany in November1906 regarding what he named "a peculiar disease of the cerebral cortex" and published it the following year. Neither the report at the meeting nor the publication received the deserved attention by the scientific community at the time.

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After its initial description, AD was considered an early-onset (or presenile) dementing disease. It was more than six decades before scientific research showed that AD was also the principal cause of nonspecific "senile dementia" (commonly called "cachexia"). This, in turn, has been for many years associated with cerebral arteriosclerotic disease, therefore the term "sclerosed" to commonly refer to the patients.

AD is the leading cause of dementia, accounting for about 60% of cases. Thus, based on ADI estimates, there could be projected approximately 28 million people with AD in 2015, 45 million in 2030, and 79 million in 2050 worldwide. In Brazil, it was estimated that there are about 1 million people with AD.

There is, especially in low- and middle-income countries, difficulty perceiving Alzheimer's disease as a medical condition because the initial symptoms are still taken, out of ignorance or cultural bias, as part of normal aging. This also occurs in high-income countries but to a lesser extent.

There are two forms of AD: (1) the "sporadic," with onset during senescence, which results from a genetic predisposition associated with the action of nongenetic or environmental factors, and (2) familial autosomal dominant AD (FAD), with early onset, in which the presence of a gene mutation with a Mendelian pattern of inheritance determines the occurrence of the disease. Fortunately, the FAD form is rare, accounting for less than 1% of cases.

Another way to classify AD is according to the age of onset, into late-onset AD (LITAD, onset ≥65 years) and early-onset AD (EADIP, onset <65 years). DAIT accounts for over 95% of all cases and DAIP for 1–5%. Many of the cases of DAIP are FAD.

2.1.1 Pathophysiology

In the late 1960s, studies began to occur to elucidate the etiology and pathophysiology of AD. However, although advances have been made in the knowledge of pathophysiological mechanisms, it is still unclear what exactly causes and how the disease develops and produces the varied cognitive and behavioral symptoms. It is known, however, that pathophysiological events begin to occur about 15 years before the onset of symptoms.

2.1.1.1 The Cholinergic Hypothesis

In the 1970s and 1980s, studies demonstrated substantial deficits in the neocortex of choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine (ACh) synthesis; reduced choline uptake, necessary for ACh synthesis; reduced ACh release; and loss of cholinergic neurons of the nucleus basalis of Meynert, located

at the base of the brain. These findings confirmed the occurrence of a substantial presynaptic cholinergic deficit in the brains of the patients. Subsequent research has demonstrated the role of ACh in learning and memory and the association of cholinergic dysfunction with cognitive disorders and with amyloid plaques.

From this body of knowledge arose the "cholinergic hypothesis" of AD, according to which the degeneration of cholinergic neurons in the base of the brain (which project to the neocortex and the hippocampi) is associated with the loss of cholinergic neurotransmission in those areas, among others, which contributes significantly to the deterioration in cognitive functions.

There is also a reduction in other neurotransmitters, such as serotonin, which is associated with the occurrence of behavioral symptoms of the disease.

2.1.1.2 The Amyloid Cascade Hypothesis

The most accepted hypothesis is the so-called "amyloid cascade." According to it, the initial pathophysiological event is the abnormal processing of APP, with the production of the Aβ peptide. Thereafter, hyperphosphorylation of tau protein, neuronal and synaptic degeneration, and cholinergic neurotransmission deficit would occur.

APP, whose normal function is not yet fully known, is a neuronal transmembrane localization protein, having a short portion in the intracellular medium and a long one in the extracellular. Its metabolism occurs by a double cleavage involving three families of enzymes called secretases (α, β, and γ). Initially, it undergoes a breakdown by the action of α-secretase or β-secretase and then another breakdown by the action of γ-secretase. The normal proteolytic pathway is the one initiated by α-secretase, in which there is no formation of Aβ, and therefore, it is called non-amyloidogenic. In the amyloidogenic pathway, the first cleavage is performed by β-secretase, and there is a production of the Aβ peptide; its isoforms with 40 and 42 amino acids are the most pathogenic, especially the latter.

Aβ peptide can accumulate in the extracellular environment in the form of PS but can also be found in the form of soluble oligomers that have been characterized as also very neurotoxic in recent studies. Their presence causes dysfunction and then synaptic degeneration.

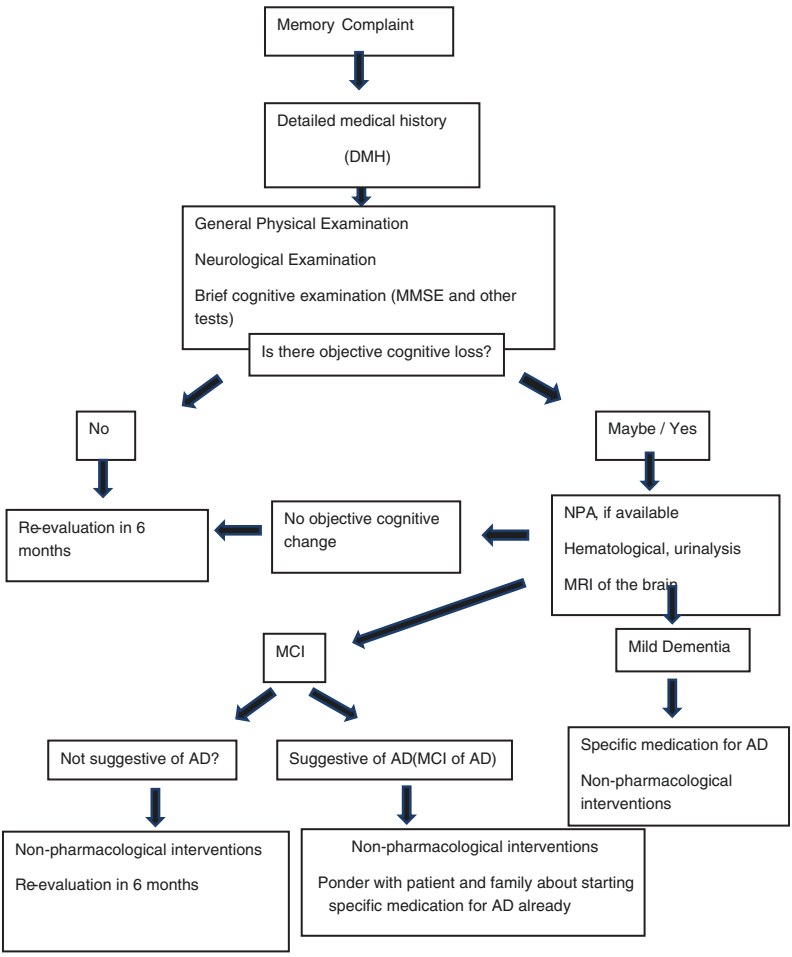
Most authors believe that Aβ peptide is involved in the hyperphosphorylation of tau protein, which causes a destabilization and destruction of intracellular microtubules, producing the NFT. This event is associated with the neurotoxicity of the Aβ peptide itself.

The knowledge of the events of the amyloid cascade has underpinned the main lines of research regarding the treatment of AD. However, it must be emphasized that this is a hypothesis, which is not sufficient to explain the entire pathology and clinical presentation of the disease. It is not even determined yet if amyloid formation is the initiator of pathophysiological events or if it is a consequence.

2.1.2 Diagnosis

The flowchart below illustrates a sequence in the basic clinical investigation of cognitive losses, with the purpose of diagnosing AD and initiating treatment. Other tests may be used according to need and feasibility, at the discretion of the physician.

Flowchart *Algorithm* of basic clinical investigation for diagnosis of Alzheimer's disease and initiation of treatment



Note: MCS Memory Complaint Scale; *MMSE* Mini Mental State Examination; *NPA* Neuropsychological Assessment; *MRI* magnetic resonance imaging; *MCI* mild cognitive impairment; AD

2.1.3 Treatment

The number of individuals with dementia is predicted to increase threefold by 2050 if demographic trends continue as they are. This is important to recognize that while the therapeutic effects of individual interventions are modest given the different areas affected by dementia, these data can be magnified if we look at the large impact that small differences make on patients' quality of life. This can be further multiplied if one considers the size of the population that can benefit from these therapeutic interventions, making dementia therapies one of the most important areas of medicine in service not only to humanity but to society as a whole [1].

With regard to slowing the progression of dementia, there is a rationale that slowing cognitive decline may imply that quality of life is maintained for a longer time. Stopping the progression of dementia even before symptoms appear would imply a cure, which currently does not exist.

Reversing the damage already done to the brain has been the target of most current research and involves reducing the rate of amyloid or tau production, reducing amyloid or tau toxicity, increasing amyloid or tau clearance, reducing neuroinflammation, and reducing neurodegeneration.

We should first be aware of medications that cause impairment of cognitive functions. Anticholinergic medications require special attention because these can cause delirium and are known to increase the risk of dementia [2, 3].

Benzodiazepines are known to cause amnestic effects, even at low doses, and long-term use of benzodiazepines has been shown to be associated with Alzheimer's disease [4].

Theoretically, the treatment of dementia should be determined by its cause. However, the greatest effectiveness of dementia treatment depends on how early it is started [5].

Acetylcholine plays an important role in memory and attention. In Alzheimer's disease, the basal forebrain, which is a major source of cortical cholinergic input, is severely affected. In this context, acetylcholinesterase inhibitors have emerged as an important therapeutic option for dementia as they increase acetylcholine levels and are FDA approved for the treatment of Alzheimer's disease [1].

The acetylcholinesterase inhibitors approved for treatment in Alzheimer's disease are donepezil, rivastigmine, and galantamine. These three acetylcholinesterase inhibitors are thought to be approximately equivalent to each other [6].

In patients with Lewy body dementia and Parkinson's disease dementia, the response to acetylcholinesterase inhibitors is particularly favorable. The picture in patients with frontotemporal dementia, on the other hand, is not as satisfactory as in the cases described above [1].

The most common side effects include nausea, vomiting, and diarrhea and are one of the most common reasons for discontinuation of these medications. Regarding gastrointestinal side effects, an alternative is a rivastigmine patch. Rarer but more serious adverse effects include syncope, bradycardia, and falls [7–9].

Discontinuing the use of acetylcholinesterase inhibitors in the advanced stages of dementia is not recommended as they will continue to make benefits even in advanced stages [10, 11].

Regarding the moderate to severe stages of dementia in Alzheimer's disease, the use of memantine is recommended. Memantine is an NMDA (N methyl D aspartate) receptor antagonist. Although it is considered a neuroprotectant, since it prevents NMDA receptor hyperstimulation, memantine has no benefit in mild forms of Alzheimer's disease [12].

There is no evidence of memantine's effectiveness in cases of vascular dementia and in Lewy body dementia and Parkinson's disease dementia [12, 13].

The most common neuropsychiatric symptoms in dementia include delusions and hallucinations. In this context, it is mandatory to investigate whether the symptoms are secondary to other infectious or toxic-metabolic causes or whether there were possible triggering factors such as sleep deprivation, loss of circadian rhythm, or change in the environment to which the patient was accustomed [1].

The commonly used approach to psychological and behavioral disorders of dementia includes antipsychotics, antidepressants, and acetylcholinesterase inhibitors [14, 15].

Concerning acetylcholinesterase inhibitors, scientific evidence has shown beneficial effects of donepezil and rivastigmine [16]. The latter is particularly favorable in cases of Lewy body dementia [17].

The use of antipsychotics in dementia should be very judicious as previous studies have shown an association with several adverse effects such as fractures, pneumonia, stroke, myocardial infarction, and acute renal failure [18, 19]. In addition, antipsychotics can trigger extrapyramidal symptoms and sedation [20].

Usually, the choice is made for atypical antipsychotics such as quetiapine, aripiprazole, risperidone, and olanzapine. Among the less sedative, risperidone stands out. The least anticholinergic is olanzapine [20].

In cases of Lewy body dementia and Parkinson's disease dementia, clozapine is the most indicated but requires frequent hematologic monitoring for the risk of agranulocytosis [21].

Typical antipsychotics should be avoided in Lewy body dementia and Parkinson's disease dementia, as they may worsen motor and behavioral symptoms, in addition to the increased risk for a serious and potential neuroleptic sensitivity reaction [22, 23].

Considering other neuropsychiatric symptoms in the context of dementia, depression stands out. Depression can affect attention, memory, motivation, and speed of processing ideas. The first episode of a major depressive disorder is usually associated with significant cognitive symptoms and, in some cases, may even characterize "pseudodementia" which is even considered as a dementia prodrome [24].

In this context, the importance of depression and its diagnosis and treatment in dementia is extremely important. This is because depression is a risk factor for both developments of Alzheimer's disease and the transformation of mild cognitive deficit into Alzheimer's disease [25].

Depression in the context of dementias has an endogenous component related to the physiological brain changes resulting from neurodegeneration, as well as a reactive component, which is the reaction to cognitive worsening and loss of independence [8].

Consequently, depression in the context of dementia is considered a treatment-resistant depression. Selective serotonin reuptake inhibitors are the first choice in the population context, but there is no evidence of their benefit in specific cases of patients with dementia. Therefore, the therapy of choice will depend on the comorbidities of each patient and should be individualized on a case-by-case basis [21, 26].

Among other factors that greatly affect cognition and are often associated with dementias are sleep disorders. Parasomnias, REM sleep behavioral disorders, and daytime hypersomnia are features that are quite present in Lewy body dementia and dementia associated with Parkinson's disease [27].

Benzodiazepines should be avoided because of their risk of falls, delirium, and cognitive dysfunction. Tricyclic antidepressants and antihistamines have anticholinergic effects and should be avoided in patients with dementia, especially in patients with Parkinson's disease dementia and Lewy body dementia [15].

A meta-analysis with 15 randomized clinical trials demonstrated that efficacy is highest for risperidone, followed by aripiprazole and olanzapine, respectively [1, 15].

Common side effects of antipsychotics include anticholinergic effects, hyperprolactinemia, QR interval prolongation, orthostatic hypotension, weight gain, metabolic syndrome, diabetes, drowsiness, sexual dysfunction, seizures, cognitive decline, and increased risk of cerebrovascular events.

In this scenario, risperidone is most responsible for causing hyperprolactinemia. Olanzapine causes the most weight gain, metabolic syndrome, diabetes, orthostatic hypotension, and drowsiness but is the least anticholinergic [1, 28].

Regarding antipsychotics in general, both typical and atypical antipsychotics are associated with an increased risk of death and should be used with great discretion. Data indicate that the risks are even higher with haloperidol, and patients with Lewy body dementia are particularly sensitive to adverse effects with antipsychotics [28].

2.1.4 Lewy Body Dementia and Dementia in Parkinson's Disease

The treatment of Lewy body dementia remains one of the most challenging in the context of dementias. This is because the combination of cognitive, neuropsychiatric, motor, and autonomic disturbances present in Lewy body dementia and Parkinson's dementia is much more exuberant than in Alzheimer's disease. This implies functional worsening, negatively impacting the quality of life of patients. Additionally, treatment of neuropsychiatric symptoms may involve exacerbation of parkinsonism, while L-dopa and other antiparkinsonian medications may lead to exacerbation of psychiatric symptoms [7].

Regarding acetylcholinesterase inhibitors, randomized clinical trials have demonstrated the benefit of rivastigmine in Lewy body dementia and dementia in Parkinson's disease [13, 16]. Consequently, there is a level of evidence type I and grade A recommendation for the benefit of rivastigmine in Lewy body dementia and Parkinson's disease dementia [7, 13, 16].

2.1.5 Frontotemporal Dementia

Clinical treatment for frontotemporal dementias is supportive only focusing on the relief of neuropsychiatric and motor symptoms with antidepressants and dopaminergic modulation therapy, respectively. Response to dopaminergic agonists is low [29].

2.1.6 Vascular Dementia

Therapeutic strategies in the context of vascular dementia focus primarily on cardiovascular and cerebrovascular risk factors [7]. The use of acetylcholinesterase inhibitors would be recommended in cases of mixed dementia. In the purely vascular dementia context, autopsy-based studies have shown that loss of cholinergic function was only present in patients with vascular dementia simultaneous with Alzheimer's disease and that cholinergic activity might even be increased in patients with dementia and multiple prior ischemic infarctions [30, 31].

2.1.7 Alzheimer's Disease

Alzheimer's disease is, pathologically, characterized by extracellular amyloid plaques, neurofibrillary tangles, and consequent neuronal death [32–34].

Regarding anti-amyloid therapy, the agent verubecestat has shown a good safety profile in early clinical trials [35]. Regarding plaques, these are composed of amyloid-beta, a product of cleavage of the amyloid-beta precursor protein. The beta-amyloid precursor protein is progressively cleaved by beta-secretase (BACE 1) and, then, by gamma-secretase to form amyloid-beta [36].

Therapeutic interventions aimed at removing amyloid plaques are one strategy to slow the progression of Alzheimer's disease. Recent and current models of the disease suggest that amyloid-beta protein triggers the pathophysiological process determined by tau protein, with a complex and synergistic interaction between amyloid-beta and tau proteins, triggering a cascade that leads to the progression of neurodegeneration and the advancement of Alzheimer's disease [37, 38].

In this context, donanemab is a humanized IgG1 antibody that acts by targeting an N-terminal chain epitope of amyloid-beta pyroglutamate, which is present only in established plaques [39–41].

It is specific for this epitope and does not bind to other amyloid-beta neurotransmitter sites or other receptors and has no known and demonstrated side effects so far. Currently, a phase 2 clinical trial study was published in March 2021 to evaluate the efficacy and safety of donanemab in patients with early-stage Alzheimer's disease [37, 39, 40].

There was a greater reduction in amyloid plaque level in the donanemab group than in the placebo group; however, no clear association could be demonstrated between this decrease and clinical outcomes at the individual level. The lack of effect on global tau protein load raises questions about whether amyloid-beta reduction leads to a halt in Alzheimer's disease progression [37].

This phase 2 randomized clinical trial demonstrated that in symptomatic patients with early-stage Alzheimer's disease, treatment with donanemab resulted in less functional and cognitive decline compared to placebo but at modest levels [37]. Consequently, larger-scale follow-ups and clinical trials are needed to prove whether donanemab prevents disease progression in symptomatic patients with early-stage Alzheimer's disease. In this context, TRAILBLAZER-EXT (ClinicalTrials.gov number, NCT04640077) is currently recruiting participants [37].

Regarding neurofibrillary tangles, these are composed of hyperphosphorylated tau protein. Under normal conditions, tau protein promotes the stabilization of microtubules. When hyperphosphorylated, tau proteins accumulate in tangles composed of helical filaments [33].

The amyloid cascade hypothesis holds that amyloid-beta accumulation dysregulates neuronal synaptic function, creating intracellular conditions for the formation of neurofibrillary tangles, triggering neuronal loss and consequently impaired neurotransmission [32].

The loss of cholinergic neurons in the basal prosencephalon is also hypothesized to create a cholinergic deficit that contributes to the memory loss present in Alzheimer's disease [34].

These complex pathophysiological processes may occur sequentially and simultaneously in Alzheimer's disease [32, 42]. Considering that the amyloid production cascade depends on the cleavage of the beta-amyloid precursor protein by beta- and gamma-secretases, inhibition or modulation of these secretases becomes a therapeutic strategy for decreasing amyloid-beta production and consequently slowing cognitive decline [43].

Beta-secretase inhibition (BACE) reduces amyloid-beta production, and BACE1 inhibitor molecules are currently available orally and have proved to be beneficial in reducing amyloid-beta protein in animal models. However, early clinical trials demonstrated toxicity, which prevented BACE inhibition from being considered a therapeutic option [44].

In this context [45], developed an antibody with a high affinity for the allosteric region of BACE1, so as not to directly interfere with other BACE substrates.

Efficacy studies show that the antibody crosses the blood-brain barrier; however, for therapeutic success, the existence of brain parenchyma capable of capturing the antibody is required [45].

Considering the tau protein, intracellular fibrillar tangles are known to lead to neuronal death. To prevent excessive activation of the microglia and consequently decrease the immune response [46], developed a humanized monoclonal beta-amyloid antibody with IgG4. This IgG4 anti-beta amyloid antibody, named MABT, has been shown in phase 1 clinical trials not to produce vasogenic edema in patients, even in patients with the ApoE4 genotype who have a higher risk for vasogenic edema. This immunotherapy is currently under the name crenezumab by the Genentech and Lily companies [47]. Initial studies on anti-tau therapeutics have demonstrated a good safety profile and safe immune response in humans [48]; however, its use in clinical practice still lacks more robust clinical trials and scientific evidence [49]. Regarding immunotherapy [50], demonstrated promising results in phase I clinical trials of the monoclonal antibody aducanumab to decrease amyloid-beta deposition and consequently slow cognitive decline. Initial success with aducanumab in early and mild cases of Alzheimer's disease indicates that treatment should begin in the earliest stages of the disease [50, 51]. In the studies evaluated to date, aducanumab has demonstrated a reduction in the level of amyloid plaques in the brain in a time- and dose-dependent pattern. Consequently, on June 7, 2021, the FDA approved aducanumab for the treatment of Alzheimer's disease using Accelerated Approval, a pathway in which the FDA approves a medication for serious and life-threatening diseases based on disease marker endpoints, in this case the decrease in the level of amyloid plaques. However, in this scenario, pharmaceutical companies must conduct phase 4 clinical trials (confirmatory trials) after approval to verify the clinical benefit. If the phase 4 trials do not confirm the clinical benefit from reduced amyloid plaque levels, FDA regulatory procedures withdraw the drug from the market (https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease). These early results have encouraged researchers to develop new therapeutic strategies to slow symptoms in Alzheimer's disease. Additionally, it has been shown that neurodegeneration is not reversible, directing therapeutics only to molecular targets such as preventing amyloid-beta deposition. Consequently, the current focus has been on new preventive strategies in the earlier stages of the disease, which represent a promising horizon for Alzheimer's treatment.

2.2 Non-pharmacological Treatment

Techniques aimed at cognitive stimulation and specific skills training may be effective in the cognitive treatment of patients with mild to moderate AD when associated with anticholinesterase.

Non-pharmacological strategies may be beneficial in treating neuropsychiatric symptoms, including educational interventions, neuropsychological rehabilitation,

cognitive training, occupational therapy, physical therapy, music therapy, and physical activity, among others.

However, although there are indications that these therapeutic approaches may be beneficial, besides not presenting the risks of drug treatment, there is still not enough scientific evidence to allow definitive conclusions. This is because to date, most studies are uncontrolled, include few subjects, and use protocols that are not well designed.

Neuropsychological rehabilitation is a non-pharmacological behavioral treatment that aims through cognitive difficulties and abilities to promote improvement by adopting strategies of compensatory and/or restorative measures [52]. These methods involve compensatory techniques (learning strategies that minimize cognitive demands) or employing cognitive skills repeatedly until premorbid performance levels are achieved.

2.2.1 Therapies for Improved Cognitive Functioning

Of the techniques and therapies for improving cognitive functioning, Clare and Woods (2004) classified treatments into three categories: cognitive stimulation, cognitive training, and cognitive rehabilitation.

Studies [53, 54] suggest that cognitive stimulation can produce substantial improvements after daily functioning training in Alzheimer's patients. It has also been shown [55] in a multicenter, randomized trial that pharmacological therapy associated with cognitive and motor stimulation produced cognitive and mood improvement in patients with mild to moderate AD after 1 year of treatment.

The rationale justifying the employment of cognitive enhancement therapies for AD is the concept of neuronal plasticity. The aging process causes gradual loss of brain systems, including impaired functioning of the neuromodulatory system. In contrast, even in the elderly, the nervous system can reorganize itself and promote the structural organization in response to the environment to adapt to new circumstances.

Brain training can strengthen the neuromodulatory systems that control learning by stimulating cortical representations at the molecular and synaptic levels, as well as the neural network. A study using stimulation techniques and PET demonstrated that seniors with memory complaints undergoing a 14-day mental stimulation program showed improved verbal fluency and decreased activity in the left dorsolateral prefrontal cortex after performing verbal memory training associated with exercise, stress reduction, and a healthy diet [56].

I. Cognitive Training

Cognitive training (CT) is designed for patients who have sufficient cognitive resources for a therapist or a computer program to guide them in exercising and practicing tasks designed for specific exercises to stimulate cognitive functions or to stimulate relatively intact cognitive functions or work on more impaired cognitive

abilities. CT is based on the assumption that practicing a cognitive ability has the potential to improve or at least maintain the performance of that trained cognitive domain.

II. Cognitive Rehabilitation

Cognitive rehabilitation (CR) is a comprehensive program using multiple approaches. It encompasses cognitive stimulation, cognitive training, and other approaches in the biopsychosocial context [57]. In CR, the patient's behavioral and social functioning are considered in the treatment [58]. CR programs in AD should aim at task training applied to the context of the patient's daily life [59].

Thus, CR in AD seeks to identify and help the patient learn and practice methods of compensation so that cognitive difficulties are minimized. This type of compensation can vary, for example, on how to organize finances and to learn to use calendars or computer and paper and pencil resources to organize and recall important information such as medications. Compensatory methods don't just involve helping memory difficulties. Patients are trained to be able to make use of external supports through learning by repetition, through repeated practice, with verbal instructions and physical demonstrations so that they can learn and master compensatory techniques that can then be applied to other situations.

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Chapter 3
The Viability of Treatment Conditioned to the Pathophysiology of Alzheimer's Disease

Fabricio Ferreira de Oliveira

3.1 Cholinergic Hypothesis

3.1.1 The Cholinergic Hypothesis and the Metabolism of Acetylcholine

A progressive decline in cognition and functionality is the hallmark of Alzheimer's disease, with considerable impacts on behavior and caregiver burden [21]. Reduced levels of acetylcholine receptors and loss of cholinergic neurons are among the major neuropathological events with neurochemical implications in Alzheimer's disease [4]. In view of the modest symptomatic effects of cholinesterase inhibitors over the clinical manifestations of this dementia syndrome, as well as possible reduced brain atrophy resulting from such therapy [38], the cholinergic hypothesis has been one of the dominant hypotheses to explain the pathophysiology of Alzheimer's disease in the past three decades. With the exception of memantine, an uncompetitive NMDA receptor antagonist that was introduced in 2003, no drug classes other than cholinesterase inhibitors have been unconditionally approved for primary therapy of Alzheimer's disease so far [20].

Whereas acetylcholine is one of the major neurotransmitters of the brain, cholinergic synapses are ubiquitously distributed in the central nervous system [38]. Two enzymes are involved in anabolism and catabolism of acetylcholine, respectively (see Fig. 3.1): choline acetyltransferase and acetylcholinesterase.

Choline acetyltransferase is the enzyme that catalyzes the final step of synthesis of acetylcholine. One potential therapeutic target in this pathway is the enzyme glycogen synthase kinase 3β, which is able to phosphorylate and inactivate pyruvate dehydrogenase, another enzyme that generates acetyl-CoA for Krebs cycle

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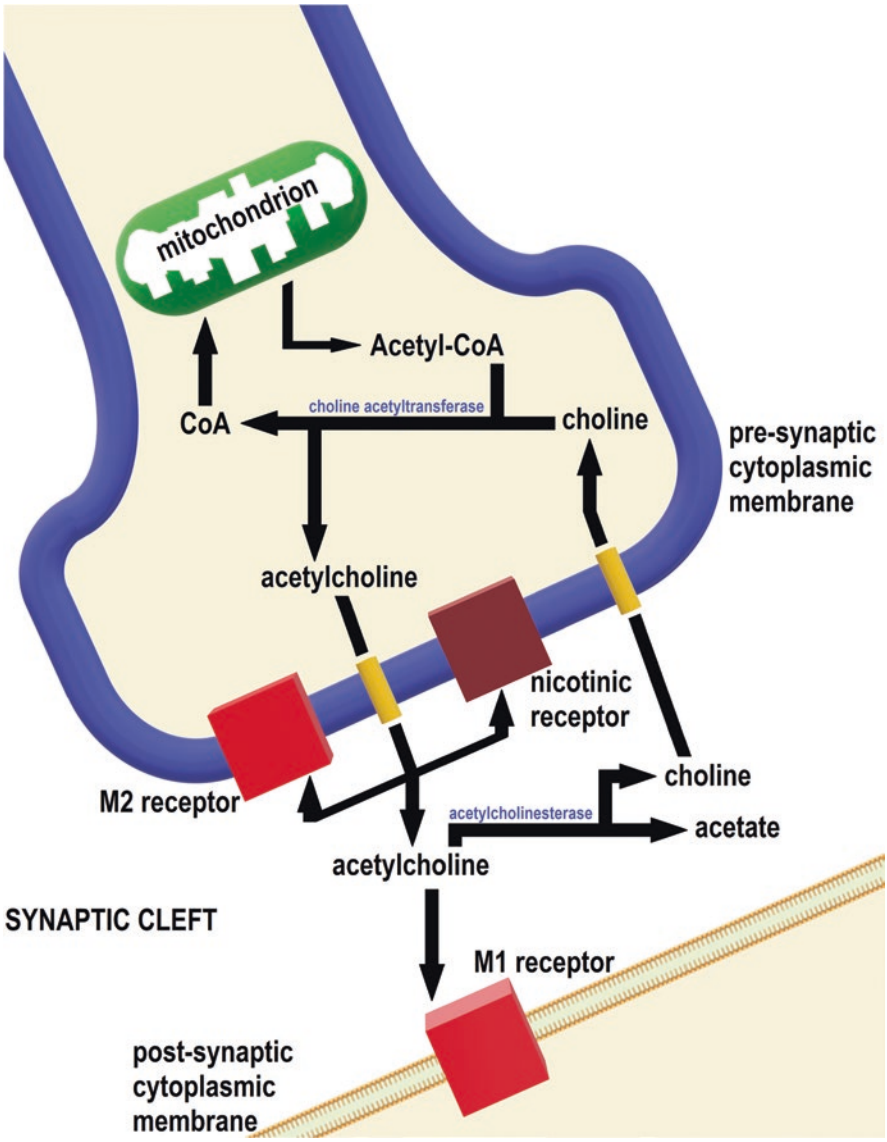

Fig. 3.1 Acetyl-CoA is produced in mitochondria by way of the breakdown of carbohydrates through the Krebs cycle. Choline acetyltransferase is the critical enzyme for the synthesis of acetylcholine, which is released in the synaptic cleft and activates postsynaptic muscarinic M1 receptors, thus transmitting a signal from the presynaptic neuron to the postsynaptic neuron. Acetylcholine also interacts with presynaptic nicotinic and muscarinic M2 receptors. Still in the synaptic cleft, the enzyme acetylcholinesterase breaks excessive acetylcholine down into choline and acetate, which are subsequently taken up again for recycling into acetyl-CoA and acetylcholine

replenishment and acetylcholine synthesis via choline acetyltransferase [12]. Acetyl-CoA is synthesized in mitochondria available in the cholinergic axons, whereas choline is actively transported from the extraneuronal fluid to the axoplasm [38]. Transport of choline is the limiting step in the biosynthesis of acetylcholine, which is then stored in the synaptic vesicles.

After acetylcholine is released into the synapse, it activates postsynaptic M1 muscarinic receptors, thus signaling the subsequent neuron [73]. The excess neurotransmitter in the synaptic cleft is hydrolyzed in less than one millisecond by acetylcholinesterase, usually available on the surface of the postjunctional membrane [38]. Acetylcholinesterase breaks acetylcholine down into choline and acetate, which are subsequently taken up for recycling into acetyl-CoA [47].

Specific biomarkers of synaptic degeneration have been identified, such as neurogranin, SNAP-25, and synaptotagmin, which can be detected in the cerebrospinal fluid and may be associated with cognitive decline and brain atrophy [16].

The cholinergic hypothesis envisages that in patients with Alzheimer's disease, neurofibrillary degeneration of cholinergic neurons located in nuclei from the basal forebrain (and particularly in the nuclei basalis of Meynert) disrupts neurotransmission in presynaptic cholinergic terminals located in the limbic system and in the neocortex as a whole [6]. These neurodegenerative mechanisms compromise hippocampal function and particularly long-term potentiation, leading to memory disturbances, and then impair other higher cortical functions, eventually leading to behavioral disturbances as well; behavior and functionality depend upon frontal lobe function, resulting in functional decline when impaired [19]. Measures of synaptic density correlate better with dementia stage than amyloid-β or tau pathology because synaptic function underlies cognitive performance [16], while synaptic dysfunction precedes the physical degeneration of the synapses [70]. Synaptic degeneration may be a result not only of amyloid-β oligomer toxicity but also of phospho-tau which may be observed in both presynaptic and postsynaptic regions [16].

3.1.2 Pharmacological Implications of the Cholinergic Hypothesis

The cholinergic hypothesis is supported by the fact that use of anticholinergic drugs has been consistently associated with functional impairment, especially in older patients with prodromal disease [8].

The basic pharmacological property of cholinesterase inhibitors consists of the inhibition of acetylcholinesterase, thus resulting in more availability of acetylcholine in the nervous system due to diminished catabolism [4]. Cholinesterase inhibitors also induce the release of other neurotransmitters, such as noradrenaline and dopamine, but their cognitive effects may vary according to individual features such as age, education, genetic background (particularly *APOE*-ε4 carrier status), number of concomitant medications, and baseline functional status [72]. Nevertheless,

the hypothesis that responsiveness to cholinesterase inhibitors could be improved by simultaneous administration of specific vitamins has not been confirmed [5].

The enhancement of cholinergic neurotransmission attributed to cholinesterase inhibitors not only produces cognitive and functional effects but also leads to behavioral improvement. These drugs have been shown to enhance REM sleep and reduce low frequencies of REM sleep electroencephalogram in Alzheimer's disease, suggesting a possible action upon REM sleep-related cholinergic neurons as well as a potential role of REM sleep alpha power to predict cognitive benefits of these drugs [54]. Still, soluble amyloid-β is known to decrease during sleep and increase during wakefulness [23] supposedly because sleep induces increases in the volume of interstitial space, leading to augmented efflux of amyloid-β [37]. Neuroprotective release of noradrenaline may also be stimulated by cholinesterase inhibitors, preventing the formation of amyloid-β, though neurodegeneration in the locus coeruleus may progressively lower the concentrations of noradrenaline [73].

In mild cognitive impairment, it is postulated that hippocampal and frontal cortical upregulation of choline acetyltransferase activity may reduce the efficacy of cholinesterase inhibitors, thus explaining why these medications are usually ineffective for such patients [39]. Moving on to a different pathway, acetylcholinesterase may be a component of aggregated structures that result in the formation of neurofibrillary tangles [13].

Therapies targeting neuroplasticity mechanisms could be relevant in view of the fact that cholinergic neurons in the basal forebrain, hippocampus, and neocortex are highly susceptible to stimuli that lead to synaptogenesis, remodeling of synapses, axonal and dendritic structures, and further neurogenesis [51]. Neurotrophins such as nerve growth factor and brain-derived neurotrophic factor could be particularly important for that.

3.1.3 Impact of Cerebrovascular Risk Factors on Cholinergic Activity

Cerebrovascular disease affecting the white matter has been shown to disrupt the cholinergic pathways that originate from the nuclei basalis of Meynert, thus consisting an important etiological factor for cognitive impairment [45]. Furthermore, reductions in cerebral blood flow and hypoxia affect syntheses of ATP (diminishing Na^+K^+ ATPase activity) and several different proteins, which are required for the generation of action potentials and synaptic plasticity regulating learning and memory [77].

Cholinergic deafferentation in Alzheimer's disease may also lead to loss of cholinergic innervation of cortical blood vessels, causing cerebral hypoperfusion and, subsequently, the clinical manifestations of the dementia syndrome [41]. In addition, cholinergic deficits may cause blood-brain barrier dysfunction and alter the dynamics of arterial and perivascular lymphatic drainage of amyloid-β [38].

Cholesterol governs synaptogenesis mechanisms in the brain [26]. Altered lipid membrane homeostasis has been known to inhibit the function of neuronal glucose transporters and reduce levels of acetyl-CoA and acetylcholine, resulting in synaptic dysfunction [48]. High serum cholesterol levels have been correlated with lower long-term efficacy of cholinesterase inhibitors in Alzheimer's disease [10], whereas statin therapy could enhance the effects of these drugs when in concomitant use [63]. Statins have been shown to improve vascular reactivity and may increase regional cerebral blood flow in patients at risk for Alzheimer's disease [11].

APOE is a moderately penetrant gene that is neither a prerequisite nor a sufficient agent for development of Alzheimer's disease, possibly due to its variable expression, despite the fact that *APOE*-ε4 alleles are the most important genetic risk factors for incidence and earlier onset of late-onset Alzheimer's disease [27]. In comparison with *APOE*-ε4 noncarriers, *APOE*-ε4 carriers with Alzheimer's disease show greater deficits in cortical cholinergic activity, a greater reduction in the total number of cholinergic neurons, and loss of choline acetyltransferase activity [48]. Different apolipoprotein E isoforms have different binding affinities to amyloid-β, but the bound ligand may induce cholinergic compensatory synaptogenesis caused by entorhinal cortex deafferentation [31]. Accordingly, *APOE*-ε4 carriers are prone to lose cerebrovascular integrity with blood-brain barrier breakdown [33], while *APOE*-ε4 carrier status in epistatic interactions with *LDLR* genotypes might differentially affect neurological response to lipophilic statins [31], mostly because *LDLR* mediates the increase in the astrocytic expression of *APOE* induced by amyloid-β [12].

Drugs that interfere with cerebrovascular metabolism may benefit neurological function when they interact with cholinergic pathways. In the renin-angiotensin system, renin cleaves angiotensinogen to form angiotensin I, which is then cleaved by the angiotensin-converting enzyme to form the vasoconstrictor angiotensin II; angiotensin II binds to the AT1 and AT2 receptors resulting in elevated blood pressure when acting on vascular receptors [75], increased blood-brain barrier permeability, and blockage of hippocampal long-term potentiation in neurons [60]. Angiotensin-converting enzyme inhibitors have genetically mediated effects that lead to slower cognitive decline in patients with Alzheimer's disease by way of central or peripheral mechanisms that are not fully understood, but that do not seem to depend upon their antihypertensive properties [28]. The potassium-induced release of acetylcholine is inhibited by angiotensin II signaling through the AT1 receptor, suggesting a cognitive role for angiotensin-converting enzyme inhibitors when they stimulate the cholinergic pathways [46]. Angiotensin II also induces phosphorylation of tau and increases reactive oxygen species and inflammation in the central nervous system, while angiotensin-converting enzyme inhibitors have been shown to suppress hippocampal astrocyte activation and oxidative stress [28]. Substance P is typically degraded by the angiotensin-converting enzyme, thus angiotensin-converting enzyme inhibitors may also improve cognitive function by increasing brain substance P, which has been reported to enhance the activity of neprilysin, an amyloid-β-degrading enzyme [56]. Angiotensin II regulates the expression of *HMGCR* [12] and appears to have anti-serotonergic properties that may lead to

increased amyloidogenesis, potentially modifiable by brain-penetrating angiotensin-converting enzyme inhibitors [1]. In the periphery, angiotensin-converting enzyme inhibitors have been implicated in the modulation of glucose homeostasis and in the boosted secretion of adipokines such as adiponectin and leptin, thus augmenting insulin sensitivity and potentially slowing cognitive decline in patients with Alzheimer's disease [28].

Angiotensin-converting enzyme inhibitors consist of an important drug class that had some of its cholinergic roles suggested by pharmacogenetic studies. Pharmacogenetics may also be crucial to recognize other drug classes that might indirectly affect the main pathways involved in the pathogenesis of Alzheimer's disease.

3.1.4 Interactions of Cholinergic Pathways with Other Neurotransmitter Systems in the Brain

Glutamate is the main excitatory neurotransmitter in the nervous system, whereas NMDA receptors form glutamate-gated ion channels that require glycine as a co-agonist, are highly permeable to calcium, and mediate activity-dependent synaptic plasticity, consisting of a major class of receptors for excitatory neurotransmitters in the brain [34]. NMDA receptors appear to be tetramers with two NR1 subunits and any two of four NR2 subunits (NR2A, NR2B, NR2C, or NR2D) which modulate channel activity, while a variable NR3 family of inhibitory subunits has also been reported [14]. Cholinesterase inhibitors have synergistic effects with memantine, an uncompetitive NMDA receptor antagonist that supposedly lowers the rate of apoptosis in the central nervous system; this synergism is usually associated with longer disease duration particularly in the moderate dementia stage, but there are no differences in survival rates, and no disease-modifying effects have been proven for these drugs [21], also because cholinesterase inhibitors do not seem to affect cerebrospinal fluid biomarkers of amyloidosis and tau pathology [7]. Reduced loss of cholinergic neurons has also been reported with use of memantine, concurrent with the enhanced processing of the non-amyloidogenic pathway of the amyloid precursor protein [14]. Presynaptic nicotinic receptors facilitate the release of glutamate, while activation of muscarinic receptors may decrease the release and the concentration of glutamate in the synaptic cleft [38]. On the other hand, homocysteine is a cerebrovascular risk mediator and neurotoxic NMDA receptor agonist that potentiates the cytotoxicity of amyloid-β [12].

A cholinergic-serotonergic imbalance appears to be relevant for Alzheimer's disease pathogenesis as well. Serotonin receptor antagonists amplify the cholinergic signal associated with cholinesterase inhibitors, potentially enhancing cognition [20]. Several studies have suggested the relevance of serotonergic pathways in this dementia syndrome [73]:

- Neuropathological studies have shown that serotonin levels and serotonin receptors in general are decreased.

- Psychotic symptoms and cognition are associated with dopamine and serotonin hyperactivity in the mesolimbic system and hippocampus.
- Depression in patients with Alzheimer's disease is associated with reduced serotonin, noradrenaline, and dopamine levels in the brain stem and hippocampus.
- Memantine has 5-HT_3 antagonistic effects, which are cognitively enhancing and antidepressive.
- Agonistic effects at 5-HT_4 receptors might increase the release of acetylcholine and upregulate α-secretases, which inhibit the formation of amyloid-β.

Cholinergic activity is highly relevant for Alzheimer's disease pathogenesis, but several other neurotransmitter systems interact in concert to translate biological pathway disruption into clinical manifestations of this dementia syndrome.

3.1.5 The Cholinergic Hypothesis and the Amyloid Cascade

Interactions between the amyloid cascade and elements of the cholinergic pathways have also been described, with cholinergic receptors conceivably binding amyloid-β. Beneficial roles of amyloid-β might consist of the regulation of the uptake of choline and similar changes to vesicular acetylcholine transporter proteins to concentrate acetylcholine into the synaptic vesicles from which they are released, though deleterious actions might include the inhibition of the rapid transport of vesicular acetylcholine transporter proteins, reduced levels and function of cholinergic receptors, and reduced synthesis and release of acetylcholine [47]. Disruption of complexes between amyloid-β and receptors could be a potential therapeutic strategy for the future.

3.2 Tau Protein and Amyloid-β

3.2.1 Metabolism of Amyloid-β

One of the main pathological features of Alzheimer's disease is the anabolism of the neurotoxic and synaptotoxic amyloid-β peptide, consisting of 40–42 amino acids, which tends to accumulate in the brain as extracellular amyloid plaques or within the walls of the cerebral vasculature, subsequently increasing phosphorylation of tau, an axonal protein that binds to microtubules to promote their assembly and stability [6]. Traditional knowledge states that amyloid-β biomarkers become abnormal decades before detection of cognitive decline and also before neurodegenerative biomarkers, which become widespread later and correlate with clinical severity [42]. These theories have been challenged in recent years, in view of the fact that tau pathology can precede amyloid-β deposition at a subthreshold biomarker detection level in time, but later independent amyloid-β deposition rises above the biomarker detection threshold and accelerates tauopathy [65].

The amyloid-β 42 peptide is more hydrophobic than amyloid-β 40 and is thus prone to polymerize and form fibrils more intensely [49]. Amyloid cross-seeding or co-assembly with other proteins may occur throughout the growth of pathological amyloid structures [13]. The levels of amyloid-β depend on both its anabolic rate and its catabolism [76], while cerebrospinal fluid concentrations of amyloid-β 40 reflect the total generation of amyloid-β in the brain [32]. Actually, some studies have raised the hypothesis that amyloid-β 40 may be anti-amyloidogenic [65].

In physiological levels, amyloid-β has a neuroprotective role and induces long-term potentiation, while its pathological accumulation in the brain might not be sufficient to cause Alzheimer's disease [15]. *APOE*-ε4 carrier status increases the risk for aggregation of amyloid-β (amyloidosis) and impairment of long-term potentiation, while male sex increases the risk for neurodegeneration, both pathological mechanisms rising with age even in cognitively healthy people [43]. Clusterin (apolipoprotein J) is translated by *CLU* and seems to regulate the toxicity and the solubility of amyloid-β, potentially modifying its clearance at the blood-brain barrier [42]. The exposure of hydrophobic groups on the surface of amyloid-β oligomers (the earliest forms of amyloid-β aggregation, potentially more harmful to cognition) is a major determinant of their neurotoxicity, while amyloid fibrils are able to spread between neurons [15]. In addition, naturally occurring glycosaminoglycans, copper, and zinc ions can also induce aggregation of amyloid-β and toxic effects [6].

Table 3.1 lists the different forms of amyloid-β aggregates with their respective sizes.

In early-onset Alzheimer's disease, highly penetrant point mutations in *APP* (21q), *PSEN*1 (14q), and *PSEN*2 (1q) increase the rates of aggregation and deposition of amyloid-β 40 and amyloid-β 42 [75]. All pathogenic *APP* missense mutations are located within or near the region coding for the amyloid-β42 peptide that will be generated by proteolysis [71]. *PSEN*1 and *PSEN*2 encode the proteins that lie at the catalytic center of the γ-secretase complex [4]. Trisomy of the chromosome 21 also leads to increased production of amyloid-β due to the presence of an extra copy of *APP* [38], reaching up to a sixfold increase in plasma amyloid-β in comparison with age-matched people with only two copies of the chromosome.

Table 3.1 Different forms and sizes of amyloid-β aggregates

Structure	Diameter
Non-neurotoxic amyloid-β monomer	0.1–0.2 Å
Amyloid-β dimer	0.6 Å
Amyloid-β-derived diffuse ligands	50 Å
Amyloid-β oligomer	Variable
Amyloid-β protofilament	25–30 Å
Amyloid-β protofibril	60–80 Å
Amyloid-β fibril	70–120 Å

3.2.2 Proteolysis of the Amyloid Precursor Protein

The transmembrane amyloid precursor protein is proteolytically processed by two competing pathways [6]: a non-amyloidogenic one (α-secretase pathway) and an amyloidogenic one (β-secretase pathway). In the non-amyloidogenic pathway, the amyloid precursor protein is cleaved by α-secretase resulting in the release of a soluble form of the amyloid precursor protein, while a remaining α-C-terminal fragment (C83) is left in the membrane for further cleavage by γ-secretase into the non-amyloidogenic fragments amyloid precursor protein intracellular domain and p3. In the amyloidogenic pathway, the amyloid precursor protein is cleaved by the β-secretase BACE1 to liberate another soluble form of the amyloid precursor protein, while the β-C-terminal fragment (C99) left embedded in the membrane is cleaved by γ-secretase into the amyloid precursor protein intracellular domain and the amyloid-β 42 or the amyloid-β 40 peptides.

Cytokines such as brain-derived neurotrophic factor, interleukin-1α, and interleukin-6 may stimulate expression of *APP*, while interleukin-1β decreases it [12]. In addition, while nutrients have been shown to affect the composition of the gut microbiota as well as the formation and aggregation of cerebral amyloid-β, gut bacteria can release considerable amounts of amyloid, which might play a role in the modulation of signaling pathways and the anabolism of proinflammatory cytokines related to the pathogenesis of Alzheimer's disease [61]. Modulation of the gut microbiota and the gut-brain axis might be an effective therapeutic strategy for patients with Alzheimer's disease.

Age-related mitochondrial dysfunction might be another important element in the pathophysiology of Alzheimer's disease [51]. The amyloid cascade involves caspase enzymes that may be a downstream consequence of mitochondrial toxicity in the end, while preclinical Alzheimer's disease is a potential target for therapy. In view of the proteolytic pathways involved in cleavage of the amyloid precursor protein, the development of γ-secretase modulators (such as nonsteroidal anti-inflammatory drugs, which avoid undesired mechanism-based side effects that result from enzyme inhibition) and β-secretase inhibitors seemed promising [59]. Unfortunately, no drugs from these classes have shown therapeutic efficacy in clinical trials conducted thus far.

3.2.3 Pathogenesis of Amyloid-β Plaques

Early in life, about 90% of amyloid-β in the brain consists on amyloid-β 40; with aging, and particularly at the onset of Alzheimer's disease, insoluble amyloid-β 42 rapidly increases leading to the formation of amyloid plaques [75]. The locations of plaques tend to overlap with areas of the brain that seem to be the most synaptically active when a specific mental task is not being performed, the so-called default mode network, thus leading to greater vulnerability to amyloid-β deposition

due to increased cleavage of the amyloid precursor protein by β-secretase [64]. Cognitive reserve as a result of education, occupation, cognitive, and physical activity might regulate the transcription of *APOE* and protect against Alzheimer's disease because of less activity in these otherwise vulnerable brain regions but does not seem to affect levels of amyloidosis in the brain [69]. Contrariwise, the association of *APOE*-ε4 carrier status with lower lifetime engagement in physical activities might also be a result of greater deposition of amyloid-β in these brain regions, while highly educated *APOE*-ε4 carriers who practice leisure activities and have vascular health seem to survive similar dementia-free time to *APOE*-ε4 noncarriers [24].

After its anabolism and subsequent deposition in the interstitial fluid of the brain, amyloid-β can be degraded by one of several pathways [33]:

- By amyloid-β-degrading enzymes that are available at either the extracellular or the intracellular environment
- By leakage into the cerebrospinal fluid and further drainage into blood and lymph for clearance
- And by efflux into blood by capillaries of the blood-brain barrier

Understanding the pathways that lead to degradation and clearance of amyloid-β could potentially lead to future therapeutic targets for Alzheimer's disease.

3.2.4 Degradation and Clearance of Amyloid-β

Cerebral endothelial cells, pericytes, microglial cells, astrocytes, and neurons express different amyloid-β-degrading enzymes, such as neprilysin and the insulin-degrading enzyme, though their enzymatic activity may decline with oxidative stress [55]. Hypoxia downregulates neprilysin [77], activates γ-secretase [35], and increases the concentration of hypoxia-inducible factor 1α which mediates transcriptional increase in β-secretase expression, thus leading to amyloid-β accumulation [77]. Neprilysin, the insulin-degrading enzyme, and mitochondrial presequence peptidase are named Cryptidases because they contain a structural crypt that encapsulates and cleaves selected amyloidogenic peptides according to their conformational flexibility [52]. In particular, the matrix metalloproteinase MMP-9 and plasmin are amyloid-β-degrading enzymes that are able to degrade amyloid-β fibrils in addition to oligomers, while amyloid-β is known to boost the enzymatic activity of tissue plasminogen activator [55]. On the other hand, hyperinsulinemia may cause amyloidogenesis by way of the competition of insulin with amyloid-β for the insulin-degrading enzyme, a large zinc metalloproteinase [62]. Furthermore, *APOE*-ε4 carrier status is associated with reduced hippocampal concentrations of the insulin-degrading enzyme, thus leading to less degradation of amyloid-β [17].

Table 3.2 lists the amyloid-β-degrading enzymes and potential modulation by pharmacological agents.

Table 3.2 Amyloid-β-degrading enzymes

Enzyme	Pharmacological modulation[a]
Neprilysin	No
Insulin-degrading enzyme	Yes
Angiotensin-converting enzyme	Yes
Plasmin	Yes
Cathepsin D	No
Presequence peptidase	No
α2-macroglobulin	No
Endothelin-converting enzyme ECE-1	No
Endothelin-converting enzyme ECE-2	No
Matrix metalloproteinase MMP-2	No
Matrix metalloproteinase MMP-3	No
Matrix metalloproteinase MMP-6	No
Matrix metalloproteinase MMP-9	No

[a]Potential pharmacological modulation with currently available therapies

Clearance of amyloid-β 42 from the brain is stimulated by lipidated apolipoprotein E isoforms and occurs mostly by proteolytic degradation in view of inefficient exportation through the vasculature [49]. One important molecule in this process is α2-macroglobulin, which binds to amyloid-β and mediates degradation and transport of amyloid-β peptides [12]. Clearance of both extracellular and intracellular amyloid-β from the brain occurs at a rate that reaches 8% per hour [52].

Microglial response to amyloid plaque formation may be mediated by several different genes whose expression tends to increase [65]:

- *CR*1 blockage inhibits microglial activation and potentiates phagocytosis.
- Inactivation of *CD*33 potentiates microglial uptake of amyloid-β.
- And *TREM*2 is responsible for sustaining microglial phagocytosis of amyloid-β.

Oxidative stress stimulates microglial activation and could be a therapeutic target for symptomatic improvement.

3.2.5 Metabolism of Tau

Oxidative stress and iron-mediated toxicity have been associated with tau hyperphosphorylation and aggregation into insoluble paired helical filaments which result from the collapse of the neuronal cytoskeleton, further originating neurofibrillary tangles of which tau is the main component, encoded by *MAPT* in 17q21 [4]. Phosphorylation of tau is regulated by the balance between multiple kinases and phosphatases, causing disassembly of microtubules and, therefore, impaired axonal transport, leading to compromised neuronal and synaptic functions [6]. Tau is also bound to the plasma membrane where it is involved in transduction signaling,

and present in the nucleus, where it binds DNA and RNA and is able to influence gene expression by changing the organization of chromatin; it is also involved in synaptic plasticity and mediation of NMDA receptor phosphorylation [51]. Among the protein kinases involved in the formation of neurofibrillary tangles are glycogen synthase kinase 3β, cyclin-dependent kinase-5, and extracellular signal-related kinase-2, which could be potential therapeutic targets of kinase inhibitors [2].

In Alzheimer's disease, the number of neurofibrillary tangles correlates better with the dementia stage than the number of amyloid plaques, while tau accumulation is invariably wild type and not the result of inherited mutations, starting in the entorhinal and amygdalo-hippocampal regions and further spreading to neocortical association areas [70]. Soluble, non-fibrillar, and highly reactive forms of tau are toxic and correlate with neuron loss and cognitive decline [16]. Patterns of spatial and temporal formation of tau aggregates result from physical transsynaptic movement of aggregated tau from one neuron to another and subsequent intracellular seeding rather than intrinsic selective vulnerability of certain neurons to early endogenous tau aggregation [71]; thus, modulation of tau release or tau uptake could be promising therapeutic targets. Furthermore, glycogen synthase kinase 3β inhibition downregulates the amyloidogenic cleavage of the amyloid precursor protein and yields the dephosphorylation of hyperphosphorylated tau by the action of protein phosphatases [2]. Proper use of biomarkers for diagnosis is even more important in view of the fact that older people could be invariably suffering from Primary Age-Related Tauopathy (PART) or Age-Related Tau Astrogliopathy (ARTAG), two diseases that display prominent tau pathology but may clinically mimic Alzheimer's disease [67].

3.2.6 Clinical-Biomarker Correlations

Amyloidosis and neurodegeneration in Alzheimer's disease are estimated to start up to 30 years before the onset of clinical symptoms [6]. Nonetheless, it is possible that a third of the participants recruited for clinical studies display pathological entities other than Alzheimer's disease, unless they are properly diagnosed by way of biomarker studies [67].

Neuroimaging findings have shown that anxiety and delusions may predict amyloid pathology in patients with mild cognitive impairment, while agitation, irritability, and apathy may predict conversion from mild cognitive impairment to dementia [36]. The cerebrospinal fluid provides indirect measures of amyloidosis and tau pathology that may correlate with clinical features of patients with Alzheimer's disease, potentially explaining variations in therapeutic response. Cerebrospinal fluid levels of total tau reflect axonal degeneration, while phospho-tau is associated with the amount of intracellular ubiquitinated neurofibrillary tangles or extracellular protein levels during cell-to-cell transmission, and progressively lower levels of amyloid-β 42 reflect increasing deposition in the cerebral cortex [7]. It has been described that agitation is the most consistent neuropsychiatric symptom

to be correlated with core cerebrospinal fluid biomarkers of amyloidosis and tau pathology [66], which probably lead to changed neurotransmitter activities in Alzheimer's disease. Nonetheless, biomarker ratios are superior to amyloid-β and tau biomarkers in the prediction of neuropsychiatric symptoms [32]. Risperidone (but not cholinesterase inhibitors) has been shown to affect measures of amyloidosis in the cerebrospinal fluid [7]. Nevertheless, biomarker evidence of disease does not always translate into satisfactory therapeutic response: Divalproex sodium inhibits the activity of glycogen synthase kinase 3β and reduces tau hyperphosphorylation, development of neurofibrillary tangles, and apoptosis, but it does not delay emergence of agitation or cognitive and functional decline in patients with moderate Alzheimer's disease [68].

3.2.7 Interactions of Cerebrovascular Metabolism with Amyloid-β and Tau Pathology

Even though extracellular amyloid plaques are among the primary hallmarks for diagnosis of Alzheimer's disease, intravascular deposition of amyloid-β within the walls of small cerebral arteries and capillaries (cerebral amyloid angiopathy) causes vasoconstriction and inhibits angiogenesis, and occurs in more than 90% of the patients, contributing to oxidative stress and chronic hypoperfusion [46]. In cerebral amyloid angiopathy, amyloid-β 40 is the predominant form to be deposited in the perivascular spaces, perpetuating impaired perivascular clearance of amyloid-β [37]; massive vascular deposits of amyloid-β obliterate the arterial lumen and damage the endothelium and the basal lamina leading to ischemia [41], while the angiotensin-converting enzyme may accumulate in perivascular regions as a compensatory mechanism [55]. In the circulation, amyloid-β is mostly bound to soluble LDL receptor-related protein 1, which prevents its entry into the brain and leads to its systemic removal by the liver and, to a lesser extent, the kidneys and the spleen [77].

Cerebrovascular risk factors seem to be more important for pathogenesis of Alzheimer's disease than for other primary dementia syndromes [57]. Combinations of cerebrovascular risk factors are particularly important not only in the etiology of Alzheimer's disease but also to determine earlier onset of late-onset dementia due to Alzheimer's disease [22]. Small vessel cerebrovascular disease has a synergistic effect with amyloid-β and tau pathology early in the course of Alzheimer's disease, resulting in the association of white matter hyperintensities with medial temporal atrophy [45]. Increased deposition and impaired clearance of amyloid-β due to subclinical ischemic injuries might be important pathophysiological phenomena in preclinical and prodromal Alzheimer's disease [77].

Midlife hypertension followed by late-life hypotension (which is a result of the loss of noradrenergic neurons in the locus coeruleus leading to decreased concentration of norepinephrine in the brain) increases amyloidogenesis and tauopathy [25].

Hypotension may cause memory decline and increase cerebrospinal fluid phospho-tau in older people with previously high blood pressure because patients with arterial hypertension are more vulnerable to hypotension due to a shift in the threshold of blood pressure at which cerebral blood flow is sustained [35]. For *APOE*-ε4 carriers with Alzheimer's disease, targeting mild blood pressure elevations supposedly results in better cognitive and functional outcomes [25].

It has been shown that higher glucose levels are risk factors for dementia or changes in hippocampal volumes even in patients who do not have diabetes *mellitus*, and possibly adding to the pathogenesis of brain ischemia inducing expression of the amyloid precursor protein [18], as well as disruption of the blood-brain barrier [33]. Chronic hyperglycemia may cause overproduction of reactive oxygen species and induce amyloid-β oligomerization and tau hyperphosphorylation, particularly for *APOE*-ε4 carriers [30].

Up to 25% of cholesterol content in the body resides in the brain, mainly in its unesterified form which is locally synthesized [53]. The lipid composition of the brain is critical for maintaining the integrity of cell membranes and myelin sheaths, electrical insulation, vesicular trafficking, and synaptic neurotransmission [48]. On the other hand, amyloid-β oligomers impair both synaptic function and structure [65].

The astrocyte-secreted apolipoprotein E is involved in the transport of lipids that contribute to build the myelin sheath, while uptake of cholesterol from HDL cholesterol is a major source of its disposal to neurons [26]. Activity and expression of the intramembrane enzymes β-secretase and γ-secretase, which are involved in production of amyloid-β from the amyloid precursor protein, are likely affected by aging and the cholesterol content of the cellular membrane [48].Though high levels of cholesterol enhance neuronal toxicity of amyloid-β by increasing the formation of reactive oxygen species [53], the fact that *APOE*-ε4 carriers usually have increased total cholesterol and LDL cholesterol could be a compensatory mechanism due to their dysfunctional neural repair mechanisms [26]. It should be noted that amyloid-β is cleared across the blood-brain barrier by the LDL receptor-related protein 1, preferentially when it is unbound or bound to the apolipoproteins E2 and E3 or to α2-macroglobulin, while expression of the receptor for advanced glycation end products in brain endothelium facilitates influx of amyloid-β across the blood-brain barrier [77]. Furthermore, different isoforms of the apolipoprotein E affect not only the trafficking, aggregation, and clearance of amyloid-β but also phosphorylation of tau and its polymerization into intracellular neurofibrillary tangles by activation of glycogen synthase kinase 3β [48], while amyloid-β is known to induce the increase in astrocytic expression of *APOE* [31].

When in combination with other cerebrovascular risk factors, midlife hypercholesterolemia is usually associated with earlier onset of Alzheimer's disease [22], probably due to the fact that cholesterol seems to modulate the processing of amyloid precursor protein, leading to increased production of amyloid-β and subsequent cortical accumulation [10]. On the other hand, late-life hypercholesterolemia might also slow cognitive decline, probably due to atherosclerotic mechanisms that enhance cerebral perfusion [24].

Statins lower plasma cholesterol concentrations by blocking its biosynthesis through the competitive inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase [26]. As a drug class, the ability of statins to penetrate the brain is linked to their variable lipophilicity [60]. It has been reported that statins may facilitate amyloid-β degradation and reduce phosphorylation of tau as well as the risk of death due to Alzheimer's disease [74], but there is no strong evidence of benefits of statin therapy for this dementia syndrome. Nevertheless, mechanistic pathways by which these drugs could benefit such patients are not restricted to their lipid-lowering effects but also include their anti-inflammatory, antithrombotic, pro-angiogenic, and vasodilatory properties, the stimulation of the non-amyloidogenic pathway of the amyloid precursor protein by reduced levels of the β-secretase BACE1, the attenuated excitotoxicity due to decreased NMDA receptor function, the stimulated release of the insulin-degrading enzyme from microglial cells, and the increased secretion of neprilysin from astrocytes, thus leading to the degradation of amyloid-β [26].

Genotypes of *CETP* that lead to lower plasma levels of cholesterol ester transfer protein (a protein involved in exchange of cholesteryl esters from HDL cholesterol to lipoproteins containing apolipoprotein B, promoting the subsequent uptake of cholesterol by the liver) result in higher levels of HDL cholesterol and lower incidence of dementia associated not only with improved vascular integrity of the aging brain but also with the already described antioxidant effects of HDL cholesterol [3]. Protective variants of *CETP* might improve myelin biosynthesis in the brain and lead to greater white matter integrity, resulting in less behavioral symptoms in patients with Alzheimer's disease [27].

In late life, cerebrovascular risk factors correlate with cognitive and functional stabilization or even improvement for patients with Alzheimer's disease, possibly due to higher cerebral perfusion pressure [24]. Likewise, lower creatinine clearance has been associated with slower cognitive and functional decline [30], whereas higher coronary heart disease risk (which correlates well with the *APOE*-mediated density of amyloid plaques and neurofibrillary tangles in the brain) has been associated with slower cognitive decline in *APOE*-ε4 carriers with Alzheimer's disease, suggesting interactions between genomic effects of cerebral perfusion and hormonal changes over neurodegenerative mechanisms [58], particularly because sex seems to modulate the effects of cardiovascular risk factors over late-life cognitive and functional changes [29].

The angiotensin-converting enzyme is an amyloid-β-degrading enzyme that is reportedly overexpressed in the hippocampus, frontal cortex, and caudate nucleus of patients with Alzheimer's disease [56], possibly as a compensatory mechanism. Its activity is also increased in direct relationship with the amyloid-β load in the brains of patients with Alzheimer's disease, while higher activity of the angiotensin-converting enzyme in the cerebrospinal fluid is associated with reduced risk of brain atrophy [44]. Even though it may convert the more neurotoxic amyloid-β 42 into amyloid-β 40 [60] and degrade amyloid-β40 and amyloid-β 42 in vitro, its effects in vivo are still questionable [40]. While angiotensin-converting enzyme inhibitors might be beneficial by their actions on other pathways that favor neurotransmission and amyloid-β degradation, their effects over amyloid-β oligomers

and cerebrovascular deposition of amyloid-β (cerebral amyloid angiopathy) are still unclear [46]. Nevertheless, the *ACE* gene might modulate the effects of cerebrovascular risk factors over production of amyloid-β [4].

Angiotensin receptor antagonists target angiotensin II while sparing the angiotensin-converting enzyme [44]. It has been demonstrated that these drugs are able to preserve cognitive function as well as reduce incidence and progression of Alzheimer's disease in males compared with angiotensin-converting enzyme inhibitors [50], possibly not only by way of amyloid-β-lowering effects but also by reducing phosphorylation of tau and tau pathology as a whole [60]. Angiotensin receptor antagonists such as telmisartan and losartan, as well as thiazolidinediones such as pioglitazone and rosiglitazone, are also agonists of the peroxisome proliferator-activated receptor γ; activation of the peroxisome proliferator-activated receptor γ has been implicated in clearance of amyloid-β and decreasing activity of the β-secretase BACE1 [47].

It has been known that insulin increases the secretion of amyloid-β to the extracellular environment and stimulates phosphorylation of tau to form neurofibrillary tangles, while amyloid-β reduces the binding of insulin to its receptors [62]; therefore, it might be more healthy (in neurological terms) to treat diabetes *mellitus* with oral glucose-lowering drugs than with insulin. Glucagon-like peptide 1 receptor stimulation reduces accumulation of amyloid-β and levels of amyloid precursor protein as well as neurotoxicity [59]. Metformin is a biguanide that has been shown to decrease tau hyperphosphorylation as well as improve cognition in Alzheimer's disease [51], providing support for potential therapeutic strategies for patients with diabetes *mellitus* and/or Alzheimer's disease.

3.2.8 Interactions of Hormonal and Inflammatory Mechanisms with Amyloid-β and Tau Pathology

Hormonal mechanisms might be important elements in the pathophysiology of Alzheimer's disease and potentially modulated by pharmacological strategies. Melatonin, a potent-free radical scavenger, can be neuroprotective by inhibiting the anabolism of amyloid-β and its fibrillization and attenuating tau hyperphosphorylation [5]. Neurodegenerative mechanisms have been reported to affect the hypothalamic secretion of TRH leading to lowered TSH within the normal range and increasing the risk of Alzheimer's disease [24]. Elevated levels of glucocorticoids have been reported in patients with Alzheimer's disease, augmenting the steady-state levels of amyloid precursor protein and β-secretase as well as tau accumulation [5]. Estrogen is known to increase activity of α-secretase and protect against neurotoxicity induced by amyloid-β [12]. SIRT1, a protein of the sirtuin family of NAD+-dependent deacetylases, is also known to increase anabolism and activity of α-secretase by way of the activation of the α-secretase gene *ADAM*10 [9]. Upregulation of SIRT1 or estrogen could be therapeutic targets for symptomatic

amelioration of patients with Alzheimer's disease, leading to antioxidant, anti-inflammatory, and antiapoptotic effects, as well as sirtuin-induced mitochondrial biogenesis and neurogenesis.

Inflammation in response to amyloid-β accumulation and tau pathology is a major contributor to the neuropathology of Alzheimer's disease [47]. Amyloid-β oligomers may inhibit long-term potentiation and induce the formation of neurofibrillary tangles, thus leading to neuronal death and perpetuating inflammatory mechanisms [65]. Vascular dysfunction also determines hypoperfusion and inflammatory toxicity that increase the accumulation of amyloid-β and the hyperphosphorylation of tau in the brain [77]. Only for *APOE*-ε4 carriers, lifetime sanitary conditions have been shown to protect against cognitive decline in Alzheimer's disease, suggesting that infectious agents might be involved in the *APOE*-mediated neuroinflammatory mechanisms as well [30]. The apolipoprotein E seems to have a role in the protection of cells from region-selective oxidative stress when its different isoforms differentially affect clearance of amyloid-β, the sequestration of heavy metals, and the age-dependent regulation of glial activation [48]. Upon opsonization of amyloid-β by complement, microglial cells have been shown to elicit more effective phagocytosis via complement receptors, except when C1q is associated with amyloid-β [49]. Therapies that reduce oxidative damage may benefit these patients, such as the Mediterranean diet, which has also been associated with improved insulin sensitivity and glucose metabolism, as well as lower risk of coronary heart disease [74]. Another potentially valuable innovation is the use of nanocarriers as a strategy to overcome the resistance of the blood-brain barrier and permit the influx of drugs to the brain. Furthermore, dysfunction of the glymphatic system due to neuroinflammatory mechanisms may contribute to the deficient clearance of amyloid-β (which occurs predominantly during sleep) in the preclinical stages of Alzheimer's disease [76], particularly due to impaired efflux of amyloid-β through the semipermeable blood-brain barrier [33].

3.2.9 Interactions of Amyloid-β and Tau Pathology with Excitotoxic Mechanisms

Memantine blocks the excitotoxicity associated with chronic glutamatergic stimulation; amyloid-β toxicity is partly mediated by this excitotoxic cascade, associated with the hyperphosphorylation of tau that is required for the production of neurofibrillary tangles [19]. Interactions of amyloid-β and tau pathology with excitotoxic mechanisms include [14] the following:

- Amyloid-β generates oxidative stress and increased intracellular calcium that enhances NMDA responses and neurotoxic mechanisms mediated by glutamate in general.
- Amyloid-β can inhibit the reuptake of glutamate or enhance its release in view of the downregulation of glutamate transporters in Alzheimer's disease.

- And excessive activity of NMDA receptors is involved in tau hyperphosphorylation, thus contributing to the formation of neurofibrillary tangles.

An ideal antagonist of the NMDA receptor has to spare physiological neurotransmission while blocking the excitotoxic mechanisms associated with excessive activation of this receptor.

3.2.10 Future Prospects

All of the mechanisms involved in amyloidogenesis and tau hyperphosphorylation show that therapeutic targets should include not only these molecules but also neurons, brain endothelium, pericytes, glial cells, and the myelin sheath. However, most disease-modifying therapies have targeted the production, aggregation, and degradation of amyloid-β and tau, but translation of results from bench to bedside has not been practical so far. Numerous reasons could account for this, including the recruitment of patients in later dementia stages, and the lack of correlations of efficacy and safety with genetic background. Active immunization against amyloid-β caused encephalitis in 6% of cases [6] but also found a strong contraindication in cerebral amyloid angiopathy, which is common in older people and led to vasogenic edema and cerebral microbleeds due to blood-brain barrier breakdown [41]. Several humanized or fully human monoclonal antibodies that bind and mount an immunologic response against amyloid-β are currently being tested, as well as tau aggregation inhibitors [20]. Promising future therapeutic approaches include antisense oligonucleotides or RNAi to *APP* or *MAPT* [71]. In the end, it remains to be seen if viability of treatment is actually related to amyloid-β and tau or if other key toxic misfolded proteins should be targeted as a priority.

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Chapter 4
The Use of Esterase Inhibitors

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4.1 Galantamine

4.1.1 A Big Picture of Galantamine

Galantamine is sold as galantamine hydrobromide tablets (4 mg, 8 mg, and 12 mg) or galantamine hydrobromide ER (extended released) capsules (8 mg, 16 mg, and 24 mg). Galantamine and galantamine ER are not equivalents – the doses are

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different and the change from one to the other should be done with care. The cholinesterase inhibitor galantamine is used as a treatment for mild-to-moderate Alzheimer's disease. It has a dual mechanism of action, being a specific, competitive, and reversible acetylcholinesterase inhibitor, and it is also an allosteric modulator at nicotinic cholinergic receptor sites, potentiating cholinergic nicotinic neurotransmission. A small number of early studies showed mild cognitive and global benefits for patients with Alzheimer's disease, and several posterior multicenter clinical trials have been published with positive findings. Galantamine has a large volume clearance, low plasma protein binding, and a high bioavailability. Short-term, double-blind, placebo-controlled studies have shown that treatment with galantamine produces small improvements on cognitive tests and global measures of change in selected patients with mild to moderately severe Alzheimer's disease and that a dose of 16–24 mg/day appears to be the most efficacious and is the maintenance dose range in most countries. The magnitude of the treatment effect is similar to that of other cholinesterase inhibitors. Adverse events experienced by patients treated with galantamine are usually mild and gastrointestinal and may improve with dose reduction [1–4, 6].

4.1.2 Protocols with Galantamine

Benefits to cognitive and affective functions were greater in patients with Alzheimer's disease who receive the galantamine plus ambulatory cognitive rehabilitation, including a set of physical therapy, occupational therapy, and speech therapy for 1–2 h once or twice a week, than in those receiving galantamine therapy only [5].

A study showed that doses of galantamine of 16 mg/day were best tolerated in the single trial where medication was titrated over 4-week periods (Table 4.1), and because this dose showed statistically indistinguishable efficacy with higher doses, it is probably the most preferable initially [1, 5, 9].

According to several studies, the donepezil-memantine combination seems better than either drug alone for cognition in Alzheimer's disease or at least at Alzheimer's disease prodrome.

The doses used were:

- Galantamine 8 mg + memantine 10 mg.
- After receiving galantamine for 6 months, the patients received memantine 5–20 mg as well for 12 weeks, in an average daily dose of donepezil 7 ± 2.5 mg, while memantine was 16.7 ± 5.2 mg (average of 2 groups); this last study concluded galantamine + memantine is better than donepezil + memantine [13].

Table 4.1 Dosage of galantamine

	Starting dose	Maintenance dose	Increasing dose after maintenance	Observations
Galantamine	4 mg twice daily	Increase to initial maintenance dosage of 8 mg twice daily after a minimum of 4 weeks	Based on clinical benefit and tolerability, dosage may be increased to 12 mg twice daily after a minimum of 4 weeks at 8 mg twice daily	Take with meals and ensure adequate fluid intake during treatment Hepatic impairment: should not exceed 16 mg/day for moderate hepatic impairment. Galantamine and galantamine ER should not be used by patients with severe hepatic impairment Renal impairment: should not exceed 16 mg/day for creatinine clearance 9 to 59 mL/min. Galantamine and galantamine ER should not be used by patients with creatinine clearance less than 9 mL/min
Galantamine ER	8 mg/day in the morning	Increase to initial maintenance dose of 16 mg/day after a minimum of 4 weeks	Based on clinical benefit and tolerability, dosage may be increased to 24 mg/day after a minimum of 4 weeks at 16 mg/day	

4.1.3 Drug Interactions Involving Galantamine

Galantamine can interfere with the activity of anticholinergic medications [7]. Synergistic effect is observed when given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists [7].

Research was performed to find potential drug interactions with galantamine, and it was described that the most frequent pharmacodynamics interaction found was the interaction between cholinesterase inhibitors and bradycardic drugs (β-blockers, digoxin, amiodarone, calcium channel antagonists). A combination of atropinic drugs and anticholinergic medications leads to pharmacological antagonism and should not be administered together. Urinary incontinence is a well-known adverse effect of anticholinergic medications, and it counters the effects of atropinic drugs used to treat urinary incontinence. Atropinic drugs aggravate cognitive deficits (memory disturbances, confusion, and disorientation), can cause behavioral disturbances, and decrease cognitive performance in elderly patients due to their effects on the central nervous system. Sixty to 70% of the drug-drug interactions involving anticholinergic medications are pharmacodynamics [8].

4.2 Donepezil

4.2.1 A Big Picture of Donepezil

The piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase, donepezil hydrochloride, is sold as 5 and 10 mg tablets and also as 5 and 10 mg rapidly disintegrating tablets (RDT), and it is used for the symptomatic treatment of patients with mild, moderate, and severe dementia of the Alzheimer's type [9].

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate, such as bradycardia. The potential for this action may be significant to patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. Caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes can be associated with donepezil. It is recommended that donepezil do not be used in patients with cardiac conduction abnormalities (except for right bundle branch block), including patients presenting sick sinus syndrome and those with unexplained syncopal episodes [9].

Cholinesterase inhibitors can increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, such as those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs, including high doses of acetylsalicylic acid, should be monitored for symptoms of active or occult gastrointestinal bleeding. This drug can cause nausea and vomiting, being more frequent with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks, and have resolved during continued use of ARICEPT (see Sect. 4.4.5). Treatment with the 5 mg/day dose for 4–6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance [9].

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma maximum concentrations (Cmax) about 3 to 4 hours after dose administration. Plasma concentrations and area under the curve (AUC) rise in proportion to the dose administered within the 1 to 10 mg dose range studied (Table 4.2). The terminal disposition half-life (t1/2) is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple-dose administration, donepezil accumulates in plasma by four- to sevenfold; the steady state is reached within 15 days [9].

4.2.2 Protocols with Donepezil

Cognitive function shows improvement after increasing the dose of donepezil, so it is suggested that the dosage of this drug be adjusted based on the overall severity of Alzheimer's disease as well as the progression of cognitive dysfunction [12].

Table 4.2 Dosage of donepezil as a single agent

Drug	Starting dose	Maintenance dose	Observations
Donepezil or donepezil RDT	5 mg once daily	Increase only after 4–6 weeks doing the starting dose to decrease the incidence of adverse reactions and to allow plasma levels to reach steady state; 10 mg daily may be considered after that, and it is the maximum dose	It can be taken in the morning or evening, with or without food. Donepezil tablets should be swallowed whole with water, and donepezil RDT should be placed on the tongue and allowed to disintegrate before swallowing with water Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects In elderly women of low body weight, the dose should not exceed 5 mg/day since adverse events are more common in low body weight individuals, in patients 85 years old, and in females An initial dose of 1–2 mg IV of atropine with subsequent doses based upon clinical response can be used in case of overdose Hepatic insufficiency: the clearance of donepezil was decreased by 20% in patients with stable alcoholic cirrhosis Renal insufficiency: in four patients with moderate to severe renal impairment (Clcr <22 mL/mln/1.73 m^2), the clearance of donepezil was like that of 4-year-old and sex-matched healthy people [9]

Combination therapy was studied with memantine and donepezil. Tariot et al.'s study involved 404 patients with probable Alzheimer's disease who had received stable doses of donepezil for at least 3 months. They were randomized to receive memantine 10 mg twice daily or placebo. The 24-week study included patients over the age of 50 and with MMSE scores between 5 and 14 and was conducted at 37 US sites. Patients who were randomized to memantine treatment were titrated in 5 mg weekly increments, starting from a 5 mg dose daily to 10 mg twice daily. Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24. The primary efficacy measures were the change from baseline on the SIB and the ADCS-ADL19. Secondary outcome measures included the Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus), the Neuropsychiatric Inventory (NPI), and the Behavioral Rating Scale in Geriatric Patients (BGP). The combination therapy of donepezil and memantine for moderate to severe Alzheimer's disease was most effective in improving cognition, global assessment, activities of daily living, and neuropsychiatric symptoms, and the acceptability was slightly higher than that of donepezil and lower than that of memantine [10, 11].

4.2.3 Drug Interactions Involving Donepezil

Donepezil hydrochloride is about 96% bound to human plasma proteins, being about 75% to albumins and about 21% to alpha-1-acid glycoprotein over the concentration range of 2 to 1000 ng/mL. Donepezil hydrochloride is extensively and slowly metabolized, and it is also excreted in the urine. There are four major metabolites, two of them are known to be active, and there are several minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP450 isoenzymes 2D6 and 3A4, and it undergoes glucuronidation [9].

Donepezil can interfere with the activity of anticholinergic medications [7].

Synergistic effect is observed when given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents, or cholinergic agonists [7].

It was described that the most frequent pharmacodynamics interaction found with donepezil was the interaction with bradycardic drugs (β-blockers, digoxin, amiodarone, calcium channel antagonists). A combination of atropinic drugs and anticholinergic medications leads to pharmacological antagonism and should not be administered together. Urinary incontinence is a well-known adverse effect of anticholinergic medications, and it counters the effects of atropinic drugs used to treat urinary incontinence. Atropinic drugs aggravate cognitive deficits (memory disturbances, confusion, and disorientation), can cause behavioral disturbances, and decrease cognitive performance in elderly patients due to its effects on the central nervous system. Sixty to 70% of the drug-drug interactions involving anticholinergic medications are pharmacodynamics [8].

In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes, which, given the therapeutic plasma concentrations of donepezil, indicates little likelihood of interferences; however, it is not known whether this drug has any potential for enzyme induction. Inducers of CYP 2D6 and CYP 3A4, such as phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital, can increase the rate of elimination of donepezil. Pharmacokinetic studies demonstrated that the metabolism of donepezil is not significantly affected by concurrent administration of digoxin or cimetidine [9].

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibited donepezil metabolism in vitro, and a daily dose of 200 mg of ketoconazole can increase plasma concentrations of donepezil (administered 5 mg/day) by about 30–36% [9].

4.3 The Failure of Tacrine

Tacrine was one of the first drugs to be used for Alzheimer's disease, characterized by memory loss, cognitive disorders, and psychic changes. The success achieved by tacrine in treating cognitive and behavioral symptoms was understood as a

confirmation of the cholinergic theory of Alzheimer's disease. However, the effectiveness of tacrine for dementia symptoms remains uncertain. This can be seen in the low amount of prescription for tacrine in countries where it is approved for marketing and the lack of approval from various regulatory authorities in Europe and other countries. The uncertainty regarding the therapeutic results of tacrine may be a consequence of the difficulty in interpreting the results of clinical trials [19].

Tacrine is a drug whose mechanism of action is the inhibition of the enzyme acetylcholinesterase, which is used in the treatment of Alzheimer's dementia and can cause reversible abnormalities in liver enzymes; however, significant hepatotoxicity is uncommon. About half of patients treated with tacrine have liver enzyme abnormalities, and this most often occurs within the first 12 weeks of therapy, which resolves with drug withdrawal or dose adjustment [20].

The acetylcholinesterase (AChE) enzyme has always been considered a highly viable target for symptomatic improvement in Alzheimer's disease (AD), given the recognition of cholinergic deficit as an important, consistent, and early finding in AD. Tacrine, donepezil, rivastigmine, and galantamine have been developed and approved for the symptomatic treatment of AD [21].

Ursodeoxycholic acid reduced tacrine-induced hepatotoxicity (13 mg/kg/day for 105 days) in a pilot study in 14 patients with Alzheimer's disease. A comparative study found that serum alanine transaminase activity in 100 patients who took ursodeoxycholic acid was normal in 93% of cases, compared with 69% of patients who took tacrine alone. Regular monitoring of hepatotoxicity is necessary in patients with Alzheimer's disease where the use of tacrine has been recommended [22].

4.4 Rivastigmine

4.4.1 Pharmacology of Rivastigmine

The therapeutic class of the molecule is rivastigmine tartrate; ENA-713 is a parasympathomimetic agent or selective inhibitor of cerebral cholinesterase. The rivastigmine molecule was developed by Marta Weinstock-Rosin, professor emeritus in the Department of Pharmacology at the Hebrew University of Jerusalem, and sold to Novartis by the university's own technology transfer company, called Yissum, for commercial development. This molecule is a semisynthetic derivative of physostigmine, which is a parasympathomimetic agent of indirect action by inhibiting acetylcholinesterase. It has been available in capsules and liquid formulations since 1997. Rivastigmine was patented in 1985 and entered medical use in 1997. It was approved by the FDA (Food and Drug Administration) in April 2000. In 2006, it became the first globally approved product for the treatment of mild to moderate Alzheimer's disease and for dementias associated with Parkinson's disease [23].

The pharmaceutical forms and dosages currently available are [24]:

- Hard gelatin capsules – 1.5, 3.0, 4.5, and 6.0 mg
- Oral solution – 2 mg/mL
- Transdermal patch (patch): 5 cm^2 with 9 mg, 10 cm^2 with 18 mg, 15 cm^2 with 27 mg, and 20 cm^2 with 36 mg

4.4.2 Clinical Trials

Double-blind, placebo-controlled phase II and phase III efficacy and safety studies were performed with rivastigmine for the treatment of Alzheimer's disease. For these studies, patients with MMSE (Mini-Mental State Examination) were recruited, whose scores were between 10 and 24 points (Alzheimer's mild to moderate/severe). Already in the results of phase II, the studies showed that rivastigmine produced cognitive improvement and, according to the cognitive tests carried out in these studies, the daily activities of the patients had a positive advance. There was a noticeable improvement in the advancement of Alzheimer's disease, and it is important to emphasize that all dosages used produced an overall beneficial effect on the cognition of patients with the active drug. During the studies, some fundamental scales were used to measure this improvement, which are widely used instruments, both in the daily routine of offices and in clinical research [24]:

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is a compilation of tests, which are based on the performance of several relevant cognitive areas of the brain in patients with Alzheimer's disease, such as attention, learning, memory, and language.
- Clinical Interview-Based Impression of Change (CIBIC-Plus) is a clinical assessment of the patient's overall change in the cognitive, behavioral, and performance domains, incorporating separate patient and caregiver views. This comparison is extremely important to assess how the patient sees the reality in which he/she lives.
- Progressive Deterioration Scale (PDS) is an assessment performed only by the caregiver, measuring the patient's ability to perform daily activities, such as personal cleanliness, food, and help with household chores.

Data were collected in this study and started to appear from the 12th week of treatment, about 3 months after use with dosages between 6 and 12 mg. Cognitive improvement in global performance was observed, while patients who used placebo had cognitive worsening and global deterioration on cognitive scales, such as the ADAS-Cog., about 5 points lower than in the rivastigmine group.

Improvements in cognitive functions, such as linguistic ability, memorization, praxis, time, and spatial orientation, had improved performance. An improvement of about 15% was observed in patients who finished the 6-month treatment with

rivastigmine in these items: memorizing words, agitation, crying, delusions, inappropriate actions, hallucinations, episodes of physical/verbal violence, and tearing. Anxiety symptoms and episodes were noted.

Similar studies using cognitive scales were carried out in the patch form [24–29].

4.4.3 Carbamate

Rivastigmine is a selective carbamate-type acetyl and butyrylcholinesterase inhibitor, a parasympathomimetic agent, which facilitates cholinergic neurotransmission by the slow degradation of acetylcholine released by cholinergic neurons that have their functionality preserved, increasing the amount of this neurotransmitter in the synaptic cleft. This action makes rivastigmine have a beneficial effect on cognitive deficits, as demonstrated in the cognitive scales, as it increases the availability of acetylcholine in the cerebral cortex and hippocampus [30].

There is scientific evidence that this inhibition of the cholinesterase enzyme could also decrease the formation of beta-amyloid precursor protein (PAP) and, thus, also of amyloid plaques, which are one of the main pathological characteristics of Alzheimer's disease. An addendum: carbamates, which can also be called urethanes, are organic compounds derived from carbamic acid, nitrogenous, with anticholinesterase action, that is, capable of reversibly inhibiting the action of the enzyme acetylcholinesterase (AChE), responsible for the degradation of acetylcholine, which is a neurotransmitter, making it much more active in synaptic clefts causing cell hyperexcitation [29].

However, as described above in pharmacodynamics, rivastigmine has only a symptomatic effect and does not act on the cause of Alzheimer's disease [24].

4.4.4 Pharmacokinetics

Rivastigmine is rapidly absorbed orally, and plasma concentrations are reached in approximately 1 hour. As a result of the interaction of rivastigmine with its target enzyme, acetylcholinesterase, the increase in bioavailability is about 1.5 times greater than expected with increasing dose. The absolute bioavailability after a 3 mg dose is about 36% ± 13%. Administration of rivastigmine with food delays absorption (tmax) by 90 min, decreases Cmax, and increases AUC (area under the curve) by approximately 30% [24, 30, 31, 33].

However, transdermal absorption (adhesive/patch) is slower. After the first dose, plasma concentrations are observed after a time interval of 30 min to 1 hour after application of the patch. Plasma concentrations increase slowly and, after about 8 hours, reach levels close to the maximum; however, the maximum values (Cmax) are observed later, about 10–16 hours. After reaching the peak, plasma concentrations slowly decrease over the remaining 24 hours. When the old patch is replaced

by the new one, the initial plasma concentrations slowly decrease for approximately 40 minutes on average, until the absorption of the new application becomes faster than the elimination, and the plasma levels start to increase again and reach a new peak in approximately 8 hours. In the steady state, depression levels are approximately 50% of peak levels, in contrast to the oral dose, whose concentrations drop to virtually zero between doses. Plasma concentrations are observed with all concentrations and sizes of patches [24, 33].

The binding of rivastigmine to plasma proteins is approximately 40%, therefore weak. Rivastigmine is distributed equally between blood and plasma; in addition, the molecule easily crosses the blood-brain barrier, reaching peak concentrations within 1 to 4 hours and with a cerebrospinal fluid-plasma AUC ratio of 40% [31]. This distribution mechanism is also observed in the transdermal form. As previously mentioned, rivastigmine is rapid, with a plasma half-life of approximately 1 hour, mainly via cholinesterase enzyme-mediated hydrolysis to the decarbamylated metabolite. In vitro, the Rivastigmine shows minimal inhibition of acetylcholinesterase (< 10%). Based on in vitro studies, no pharmacokinetic drug interactions with metabolized drugs are expected by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6, and other animal studies did not show involvement of cytochrome P450 coenzymes; therefore, there was no evidence of drug interactions related to this same cytochrome in humans. The total plasma clearance of rivastigmine was approximately 130 l/h after an IV dose of 0.2 mg and decreased to 70 l/h after an intravenous dose of 2.7 mg. In the transdermal form, rivastigmine is rapidly and extensively metabolized with an apparent plasma elimination half-life of approximately 3.4 hours after removal from the transdermal patch, also via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Unchanged rivastigmine is not found in urine; renal excretion of metabolites is the main route of elimination, which is rapid and complete renal complete (> 90%) within 24 hours. Less than 1% of the administered dose is excreted in feces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease. The same type of elimination is seen in the transdermal form [24, 33].

In elderly patients, studies revealed that plasma concentrations in people over 60 years were higher when compared to younger individuals aged between 19 and 40 years, with doses of 1 mg of rivastigmine. With increasing dose, it was found that in the elderly population, plasma concentrations were about 30% higher than in a younger population. The decarbamylated metabolite did not change with the age of the patients, even those affected by Alzheimer's disease. The same was observed in patients using transdermal rivastigmine. Another population that needs more attention and care are those with renal failure, where studies have shown discrepancies in plasma levels between patients with moderate and severe renal failure, but this difference has not been clearly elucidated in these studies. What was evident is that the plasma concentrations of individuals with severe renal impairment and healthy individuals (control) were not very different, both using a dose of 3 mg. However,

individuals with moderate renal failure had 2.5 times increased plasma concentration, and decarbamylated metabolites were increased by about 50%. The same results are seen in patch form [24, 38].

In patients with mild and moderate liver failure, a plasma concentration 60% higher than in healthy individuals was observed. In this population, administration of different doses showed a mean oral clearance of rivastigmine about 60–65% lower than in healthy subjects. Pharmacokinetic changes in this type of population did not have more deleterious effects on the incidence and severity of adverse events compiled. For the transdermal form, the same effects are expected [24].

Preclinical safety studies of rivastigmine were done in relation to toxicity, mutagenicity, carcinogenicity, multiple toxicity, and reproductive and local toxicity. No signs of mutagenicity were observed in these studies; however, at higher doses, signs of chromosomal aberrations were evidenced, which the researchers concluded that this result may have been false positive and not traces of carcinogenicity, both in oral and transdermal forms. Regarding reproduction, there were no evidences of teratogenicity and adverse effects on fertility, uterine growth, or reproductive function in animals (rats) that received doses of up to 1.1 mg/kg/day. In multiple toxicity with maximum doses and different species, central and peripheral cholinergic stimulations were visualized. However, in vivo tolerability proved to be different among the species studied, with the dog being the most sensitive, even with more pronounced gastrointestinal effects. In local tolerability, mild irritation in mucous membranes and eyes was observed in rabbits. Like all medications, rivastigmine has contraindications. Its use is not recommended in patients with hypersensitivity to rivastigmine and other carbamate derivatives and excipients used in the formulation of the drug. Individuals with dermatitis or any other skin pathology are contraindicated using the patch form [24, 30, 33].

4.4.5 Adverse Events

Adverse events are expected in all use of medications: in rivastigmine, the most commonly observed were the gastrointestinal ones, such as nausea and vomiting, in about 30% of the patients observed. During clinical studies weight loss and loss of appetite were the most commonly reported events [24, 30].

According to the results of the studies, other events, less common, were observed with the use of rivastigmine capsule and oral solution:

Common adverse events, in addition to the gastrointestinal ones already reported, were agitation, confusion, nightmare, anxiety, dizziness, abdominal pain, dyspepsia, fatigue, asthenia, headache, tremors, and drowsiness. Other adverse events were observed less frequently in patients: insomnia, depression, syncope, cardiac arrhythmias, duodenal and gastric ulcers, fall, skin rash, and pruritus. Rarely, events such as hypertension, hallucinations, seizures, pancreatitis, severe (intense) vomiting

associated with esophageal rupture, hyperhidrosis, stroke, angina pectoris, and myocardial infarction were seen in patients taking the oral form.

In the transdermal form, in addition to those observed in the oral form, additional unusual events could be observed: erythema at the application site, edema, and contact dermatitis. In post-marketing, that is, when the drug is already on the market, spontaneous reports of some events were reported by users of the oral medication (oral solution and capsules); however, it is not possible to measure these frequencies nor the number of individuals involved nor the relationship with the medication in question, as these were voluntary reports of a certain population. Each country has its own agency to report such events. Spontaneous reports were dehydration, aggressiveness and agitation, extrapyramidal symptoms in patients with Alzheimer's dementia, sinus node disease, hepatitis, and Stevens-Johnson syndrome allergic (disseminated) dermatitis. In the transdermal form (adhesive/patch), urinary incontinence has been commonly reported, while other less common and rare have been reported, such as stroke, increased psychomotor activity, erythema, blisters, and edema at the application site [24, 32, 33, 36].

4.4.6 Drug Interactions

The use of concomitant medications and the drug interactions foreseen with the use of rivastigmine deserves special attention. Due to extrapyramidal symptoms, the use of metoclopramide, for example, with rivastigmine is not recommended. As described above, rivastigmine has an anticholinesterase effect and should not be administered with muscle relaxants such as succinylcholine. Rivastigmine may interfere with cholinergic medications, such as oxybutynin, physostigmine, and pyridostigmine, and also concomitant medications with rivastigmine should not be considered [24, 30, 37].

Rivastigmine should be taken away from meals.

Additive effects of bradycardia have been observed with rivastigmine and atenolol-type beta-blockers and other cardio selective beta-blockers. Smoking patients, that is, those with frequent use of nicotine, had their oral clearance of rivastigmine in about 23%. Warfarin deserves special attention, as it can present many drug interactions, when used with rivastigmine it did not increase the prothrombin time in patients using these two drugs concomitantly, in healthy volunteers [24, 36].

Drug interactions, pharmacokinetics or pharmacodynamics, which may occur with the use of commonly used and prescribed drugs such as antacids, calcium channel blockers, antihypertensives, analgesics, non-steroidal anti-inflammatory drugs, benzodiazepines, among others, were not observed in use with rivastigmine [24, 36].

4.4.7 Doses and Administration

Initial consolidated doses of rivastigmine are 1 mg, twice a day, orally and are recommended in patients especially sensitive to the effects of cholinergic drugs. Doses of 1.5 mg, twice a day, orally are commonly used in the initial treatments of Alzheimer's disease. Given the tolerability of patients, after 2 weeks of use, doses of 3 mg, twice a day, orally can be prescribed. Doses should be increased to 4.5 mg and 6 mg, at least after 2 weeks of treatment each, if there is no serious adverse event [35].

If treatment is interrupted due to any intolerability, smaller doses should be resumed. The capsules should not be broken or chewed; if there is a problem in swallowing, another pharmaceutical form should be chosen. The maximum dose to be taken orally is 6 mg twice a day. In the transdermal form (patch), the initial dose is 9 mg of rivastigmine (5 cm^2 patch); if well tolerated, the dose can be increased after 4 weeks to the dose of 18 mg (10 cm^2 patch). Dosage increases with the use of the transdermal patch should be made according to the tolerability of each patient, that is, the doses of 27 mg (15 cm^2 patch) and 36 mg (20 cm^2 patch). If treatment is interrupted due to undesirable events and effects, retreatment should be restarted with lower dosages, as recommended. Patches must be changed every 24 hours [24, 30, 35].

Symptoms related to Rivastigmine overdose were vomiting, nausea, diarrhea, tremors, headache, dizziness, drowsiness, bradycardia, mental confusion, hallucinations and general malaise. It is noteworthy that rivastigmine is an anticholinesterase drug and its overdose can result in cholinergic symptoms such as excessive salivation, vomiting, sweating, among others. Given the half-life of about 9 hours, it is important to remember that in cases of overdose, no other dose should be administered within the next 24 hours. Most symptoms of overdose are caused by symptomatic treatments, except in the cases that have severe adverse effects, in which the use of atropine is recommended. The use of scopolamine is not recommended for the treatment of symptoms of overdose related to rivastigmine [24, 30, 36].

4.4.8 Transdermal Use of Rivastigmine

The use of rivastigmine's patch in patients with Alzheimer's disease has the great advantage for those who are in more advanced stages and with swallowing difficulties. In addition, it is used every 24 hours, that is, once a day. However, this route of administration deserves special care, so that its effectiveness is fully satisfactory [38].

The recommendations are [24, 32, 34, 38]:

- The patch should be applied, preferably after showering, with clean, dry skin, and no hair.
- No product such as moisturizing cream, ointments, or lotion should be present at the patch application site.
- The patch must be changed every 24 hours, and its application must be in different places each day but on the upper and lower back, on the arm, or on the chest.
- It is important to ensure that application areas are free from friction and to avoid wearing tight clothing.
- The patch must be pressed at the administration site until the edges are fully adhered to the skin.
- If the patch comes off, a new one must be applied for the rest of this day, and then it must be changed for a new one the next day at the same time as the usual schedule.
- The skin of the elderly is thinner and drier, so care must be taken when removing the adhesive.
- Bathing, sun, or swimming should not affect the adhesive system. However, one must be careful with excessive heat.
- After removing the rivastigmine patch, fold it in half with the sticky part on the inside and press. Return the used adhesive to the original sachet, and dispose of it safely, out of reach of children. Wash your hands with soap and water after removing the adhesive.
- If there is any skin lesion, the physician must be notified promptly for a reassessment.

4.4.9 Storage

The care with the medications must be extreme, so that its effectiveness is preserved. The storage of rivastigmine in its capsule form, oral solution, or transdermal patch should be stored at room temperature, between 15 and 30 °C, in a place without humidity, without exposure to light and heat. None of the dosage forms must be frozen or cooled.

All medication must be left out of reach of people suffering from psychiatric disorders and dementias and children [24, 30].

The evolution of Alzheimer's disease is characterized by damage to various parts of the brain, and as it progresses, it causes several limitations over time, such as driving vehicles, operating machinery, and handling the stove; for example. Rivastigmine, in the first days of treatment, can cause dizziness and drowsiness, and this can cause a greater limitation for patients using this drug [24, 30, 33].

Currently, rivastigmine is still one of the few drugs used to treat Alzheimer's disease. All medications used for Alzheimer's disease neither cure the disease nor impede its progress. However, early diagnosis and treatment with already approved drugs can improve the quality of life of patients affected by this devastating disease.

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Chapter 5
Pharmacology of NMDA (*N*-Methyl-D-Aspartate) Receptor Antagonists in Alzheimer's Disease

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5.1 Glutamate and Its Receptors

NMDA is part of the group of glutamate receptors, and to understand the pharmacology involving them, we need first to understand what NMDA receptors are, which leads us to understand the role of glutamate and its receptors on Alzheimer's disease [1].

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Glutamate is the primary excitatory neurotransmitter in the brain, and it bounds to both ionotropic and metabotropic glutamate receptors. The cognitive, neurodegenerative dysfunction caused in Alzheimer's disease, clinically characterized by memory loss and changes in behavior and personality, may be caused by a destabilized synaptic Ca^{2+} handling in response to over activation of NMDA receptors [1].

Some characteristics and the most important topics that relate these receptors with Alzheimer's disease are:

Ionotropic glutamate receptors (iGluRs):

- Responsible for fast neuronal communication at excitatory synapses.
- Comprised of the subfamilies: α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and NMDARs.
- Excessive stimulation of glutamatergic signaling results in excitotoxicity.
- Glutamate excitotoxicity originates acute effects.
- There is a strong indication that glutamate excitotoxicity can cause delayed and slow neurodegeneration due to toxicity mediated by excessive Ca^{2+} entry.
- The toxicity mediated by excessive Ca^{2+} is primarily through NMDARs, since NMDARs present a much higher permeability for Ca^{2+} than other iGluRs [1].

Metabotropic glutamate receptors (mGluRs):

- Comprised of seven-transmembrane-domain proteins that link to G-proteins.
- Group I mGluRs control the levels of Ca^{2+} and cAMP second messengers—such as inositol 1,4,5-triphosphate (IP_3).
- Group I mGluRs elicit the release of arachidonic acid via intracellular Ca^{2+} mobilization from intracellular stores, such as mitochondria and endoplasmic reticulum. That facilitates the release of glutamate and can trigger the formation of neurofibrillary tangles, which is a pathology of Alzheimer's disease.
- mGluRs regulate neuronal injury and survival, possibly through a series of downstream protein kinase and cysteine protease signaling pathways that affect mitochondrially mediated programmed cell death.
- mGluRs may also play a role in glutamate-induced neuronal death by facilitating Ca^{2+} mobilization.
- mGluRs are a target for neuroprotective drug development. They represent a pharmacological path to a relatively subtle amelioration of neurotoxicity because they serve a modulatory rather than a direct role in excitatory glutamatergic transmission [2].

Since NMDA are a part of the iGluR group, this chapter will focus on iGluRs and not on mGluRs.

5.2 NMDA (*N*-Methyl-D-Aspartate) Receptors and Alzheimer's Disease

NMDA receptors are glutamate-gated cation channels. As already described in this chapter, they have high calcium permeability, which is responsible for important roles, such as developing the central nervous system, generation of rhythms for

breathing and locomotion, and neuroplasticity, being essential in the processes of learning and memory [3].

Abnormal expression levels of NMDA receptors (NMDAr), as well as their function altered, can be involved in numerous neurological disorders and pathological conditions. Hypofunction of NMDAr can result in cognitive defects; overstimulation of NMDAr causes excitotoxicity and subsequent neurodegeneration. NMDARs are important therapeutic targets for research in many central nervous system disorders, such as stroke; hypoxia; ischemia; head trauma; Huntington's, Parkinson's, and Alzheimer's diseases; epilepsy; neuropathic pain; schizophrenia; mood disorders; and even alcoholism. Drugs targeting NMDAr had limited success in the clinical practice due to poor efficacy and serious side effects, such as hallucinations, catatonia, ataxia, nightmares, and memory deficits. However, memantine was proved in trials to have excellent safety and tolerability, with a frequency of adverse events similar to placebo. A detailed understanding of the mechanisms underlying agonists of this receptor can lead to the development of more selective drugs that target specific subtypes of NMDAr, altering their function to a well-defined extent. NMDAr agonists open the NMDAr ion channel. The mechanism to channel opening is not well defined yet; however, this process can lead to interesting researches to drug development [4, 5].

5.3 Pharmacology of NMDAr and Alzheimer

5.3.1 The Big Picture and Beginning of the Clinical Use

NMDARs belong to the same class of iGluRs as AMPA (α-amino-3-hydroxy-5--methyl-4-isoxazolepropionic acid receptor) and kainate receptors. Compounds such as (*R*)-α-aminoadipate and (*R*)-2-amino-5-phosphonopentanoate were shown to be NMDAR antagonists, blocking neuronal responses to applied NMDA, but they were shown to not block responses to kainate or quisqualate. As a result, NMDARs were shown to represent a distinct subpopulation of excitatory amino acid receptors. Those NMDAR antagonists led to the discovery that NMDARs play key roles in synaptic transmission, synaptic plasticity, learning and memory, neuronal development, excitotoxicity, stroke, seizures, and other processes. NMDAR antagonists were researched to treat neuropathological and neurodegenerative diseases. However, the only NMDAR-targeted drug with satisfying therapeutic use is memantine for Alzheimer's disease. Several agents failed in clinical trials due to severe adverse effects and lack of clinical efficacy. NMDARs are still a target for research. Of the multiple drug binding sites on the various NMDAR subunits, many potential types of NMDAR antagonists exist, and some of these reveals distinct patterns of selectivity that can be interesting in the drug development [3].

5.3.2 NMDAR Pharmacology

NMDAR pharmacology has its basis in the domain structure of the NMDAR subunits. NMDARs are heteromeric (consisting of different kinds of structural subunits) complexes. They are composed of four subunits, derived from the families NR1, NR2, and NR3 subunits. Glutamate- and glycine-responsive NMDAR requires both NR1 (which contains a glycine binding site) and NR2 (which contains the (*S*)-glutamate binding site) subunits. There is evidence that each NMDAR complex contains two NR1 subunits and two NR2 subunits. The NR3 subunit can complex with NR1 subunits to form a glycine-responsive excitatory receptor that does not require L-glutamate [3].

The pharmacology heterogeneity of NR1/NR2 NMDAR complex is mostly determined by the NR2 subunit and exon 5 of the NR1 subunit.

The ion permeating channel represents a drug binding site for NMDAR channel blockers, such as memantine, as well as phencyclidine and dizocilpine. The channel is structurally related to potassium channels (one hydrophobic segment forms a P loop within the membrane, being flanked by transmembrane domains.) The P loop contributes to the selectivity filter. There is an important asparagine residue near the tip of this loop, which is important for binding several channel blockers. The other transmembrane domains contribute to the pore lining in the extracellular facing half of the membrane, contributing to channel blocker binding [3].

5.4 Memantine

5.4.1 Big Picture of Memantine

Memantine hydrochloride is allowed by FDA in the treatment of moderate to severe dementia caused by Alzheimer's disease. Oral memantine, as monotherapy or in addition to a stable dose of acetylcholinesterase inhibitors, was shown to be well tolerated during the treatment of mild to severe Alzheimer's disease for up to 52 weeks, and it generally modified the progressive, symptomatic decline in global status, cognition, function, and behavior exhibited by patients with moderate to severe Alzheimer's disease in four 12- to 28-week trials. In patients with mild to moderate Alzheimer's disease, data from three 24-week trials are equivocal, although meta-analyses indicate beneficial effects on global status and cognition. It is the only drug that acts on the glutamatergic system and is very well tolerated due to its blocking/unblocking kinetics. The mechanism of action is by persistent activation of the central nervous system NMDA receptors by the excitatory amino acid glutamate, contributing to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist, which binds preferentially to the NMDA receptor-operated cation channels. Although

memantine has good results on patients with moderate to severe dementia caused by Alzheimer's disease, there is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease. Memantine showed low to a negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine, and glycine receptors, as well as for voltage-dependent Ca^{2+}, Na^{+}, or K^{+} channels. Memantine also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency. Memantine is sold as 5 or 10 mg film-coated tablets and also 2 mg/mL solution. Following an oral administration, memantine is highly absorbed, presenting a peak concentration in about 3–7 h. Food has no effect on the absorption of memantine. The mean volume of distribution of memantine is 9–11 L/kg, and its plasma protein binding is low (45%). Memantine undergoes little metabolism, with the majority (57–82%) of an administered dose excreted unchanged in urine, and the remainder is converted primarily to three polar metabolites: N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60–80 h. Renal clearance involves active tubular secretion moderated by pH-dependent tubular reabsorption [6–9].

5.4.2 Dose and Administration of Memantine

5.4.2.1 Memantine as a Single Agent (Table 5.1)

5.4.2.2 Combination Therapy with Memantine

In vitro studies showed that memantine does not diminish the cholinesterase inhibition of acetylcholinesterase inhibitors, suggesting using combination therapy. In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine [5, 7, 10].

Although memantine has been proved to be safe in combined therapy with acetylcholinesterase inhibitors, the advantages of combined therapy are still unclear. The clinical efficacy and safety of combination therapy with acetylcholinesterase inhibitors and memantine compared to an acetylcholinesterase inhibitor alone or memantine alone in patients with Alzheimer's disease was systematically searched on the databases Embase, MEDLINE, and CENTRAL until February 2018 for eligible randomized controlled trials. The researchers pooled the outcome data using inverse variance weighting models assuming random effects, and it assessed the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the benefits of the combined therapy were inconclusive. Combination therapy had statistically significant effects on the cognition and also on the global clinical impression. However, the clinical relevance of these effects

Table 5.1 Administration of memantine as a single agent

Starting dose	5 mg/once daily	Memantine can be taken with or without food If a patient misses a single dose, they should not double up on the next dose. The next dose should be taken as scheduled If a patient does not take memantine for several days, dosing may need to be resumed at lower doses and retitrated as described The oral solution should not be mixed with another liquid. It should be administered with an oral syringe into the corner of the patient's mouth [6]
Adjusting the dose	Increase the dose in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimum recommended interval between dose increases is 1 week. *The dosage shown to be effective in controlled clinical trials is 20 mg/day* [6]	
If renal impairment	A target dose of 5 mg twice daily is recommended in patients with severe renal impairment (creatinine clearance of 5–29 mL/min, based on the Cockroft-Gault equation) [6]	
If hepatic impairment	Administer with caution [6]	

is uncertain. The overall quality of evidence was very low. With the current evidence, it remains unclear whether combination therapy has any benefit. Large pragmatic randomized controlled trials with long-term follow-up and focus on functional outcomes, delay in nursing home placement, and adverse events are needed [10].

Research was performed with mild to moderate stage patients with Alzheimer's disease already stabilized on acetylcholinesterase inhibitors. In a randomized, double-blind, placebo-controlled trial evaluating memantine in outpatients 50 years or older, with Alzheimer's disease, 216 patients were randomized to memantine and 217 to placebo. All the patients had MMSE (Mini-Mental State Examination) scores between 10 and 22. The patients received ongoing therapy with donepezil, rivastigmine, or galantamine for at least 6 months with a stable dose for 3 months prior to randomization. The primary efficacy parameters were the change from baseline in the total Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus) rating at Week 24, using the last observation carried forward (LOCF) analysis. A two-way analysis of covariance (ANCOVA) was performed with the treatment group and study center as factors and with the baseline score as covariate. Of the patients in the memantine/acetylcholinesterase inhibitors group, 89.4% completed the study, while of the patients in the placebo/acetylcholinesterase inhibitors group 88.4% completed it. The change in ADAS-Cog at Week 24 compared with baseline was 0.4 (±0.4) for the memantine/acetylcholinesterase inhibitors group, while 1.1 (±0.4) for the placebo/acetylcholinesterase inhibitors group. On the CIBIC-Plus, the scores at Week 24 were identical in both groups at 4.4 (±0.1). There was no statistically significant difference between the two groups at Week 24 in any of the secondary efficacy parameters, including Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL23) with −2.9 (±0.5) vs −2.9 (±0.6), MMSE (−0.3 ± 0.2 vs −0.7 ± 0.2), or change in Neuropsychiatric Inventory (NPI) total score with 1.1 (±0.8) vs 0.6 (±0.7) [5].

A combination therapy was studied with memantine and the acetylcholinesterase inhibitor donepezil. Tariot et al.'s study involved 404 patients with probable Alzheimer's disease who had received stable doses of donepezil for at least 3 months. They were randomized to receive memantine 10 mg twice daily or placebo. The 24-week study included patients over the age of 50 and with MMSE scores between 5 and 14 and was conducted at 37 US sites. Patients who were randomized to memantine treatment were titrated in 5 mg weekly increments, starting from a 5 mg dose daily to 10 mg twice daily. Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24. The primary efficacy measures were the change from baseline on the Severe Impairment Battery (SIB) and the ADCS-ADL19. Secondary outcome measures included the CIBIC-Plus, the NPI, and the Behavioral Rating Scale for Geriatric Patients (BGP) [5].

Well-designed studies concluded that memantine is safe and effective in modifying the progression of cognitive, functional, and global outcomes in patients with moderate to severe Alzheimer's disease, either as monotherapy or in combination with the donepezil [5].

5.5 Drug Interactions Involving Memantine and Clinical Conditions That Can Alter Its Pharmacology

No drug-drug interactions between memantine and cholinesterase inhibitors have been observed, and hence, they can be used together safely without dose adjustment to treat Alzheimer's disease [5, 6].

Memantine is a weak inhibitor of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, and a clinically relevant pharmacokinetic interaction with drugs metabolized by those enzymes is not expected. Memantine does not induce the cytochrome P450 isozymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. Memantine exerts selective inhibition of CYP2B6 activity at clinically relevant concentrations. Since memantine represents a potent, selective inhibitor of recombinant CYP2B6, it can be useful for screening purposes during early phases of in vitro drug metabolism studies with new chemical entities. Artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, and methadone are metabolized mainly by CYP2B6. CYP2B6 is one of the most polymorphic CYP genes in humans, and variants have been shown to affect transcriptional regulation, splicing, mRNA, and protein expression, as well as catalytic activity. Memantine and ketamine can also have drug interaction that can be clinically relevant due to the block open NMDAR channels via apparently similar mechanisms and can compete for the receptor, increasing the toxicity [5, 11–13].

5.5.1 Raised Urinary pH

A raised urinary pH increases the plasma levels of memantine due to its decreased urinary elimination [6].

Research showed that when the urine is alkaline with pH 8, memantine's clearance was reduced by about 80%. That leads to an accumulation of the drug and raises the possibility of adverse effects. Drugs that alkalinize urine such as carbonic anhydrase inhibitors and sodium bicarbonate may reduce renal elimination of memantine [5, 6].

5.5.1.1 Raised Urinary pH by Diet

Foods and beverages that can decrease the acid load in the human body (low or more negative renal acid load) include those abundant in potassium, bicarbonate, and alkaline minerals. Although diets including low renal acid load should be avoided or tracked while the patient is being treated with memantine, because of the increased plasma level of memantine caused by that lifestyle, diets including high renal acid load (cheese, meats, processed grains in excess) aligned with infrequent consumption of potassium and bicarbonate-rich, alkaline-forming foods (fruits and vegetables), for example, is associated with increased urinary calcium and magnesium loss, therefore originating a greater risk of osteoporosis, which is already a common concern for the specific population that is the majority of patients who present Alzheimer's disease: elderly. Research also shows the possibility of cardiovascular disease with diets that cause a high renal acid load. Diets should be managed with care, and sometimes it can be more interesting to adjust the dose of memantine than the diet of the patient. Researchers suggest that acid-heavy diets can promote cortisol production, and this elevation in cortisol can be attenuated when the acidic diet is neutralized via bicarbonate supplementation or a low-acid diet. Elevated cortisol has been associated with obesity, cardiovascular disease, and mental health because cortisol is associated with stress response [6, 14].

5.5.1.2 Renal Conditions: Renal Tubular Acidosis and Severe Infections of the Urinary Tract

Renal Tubular Acidosis

Renal tubular acidosis is caused by a defect in renal excretion of hydrogen ions, reabsorption of bicarbonate, or both. This condition occurs in the absence of or out of proportion to an impairment in the glomerular filtration rate. Renal tubular acidosis is distinguished from renal acidosis that develops as a result of advanced chronic kidney disease. This condition raises the pH of urine, increasing the plasmatic concentration of memantine, and memantine should be used with care in these patients. Plasmatic dosage of memantine in these patients is a great resource to guarantee the right protocol and dose adjustment. Clinical pharmacists can be of great value to check and monitor this plasmatic dosage together with the laboratory [6, 15, 16].

A study evaluated the pharmacokinetics of memantine in patients with Alzheimer's disease treatment and compared those with normal and impaired renal function. The study was a single-center, single-dose, open-label study. Thirty-two

patients aged 18–80 years were assigned to one of four groups (8 patients each) based on baseline creatinine clearance: normal renal function (>80 mL/min), mild renal impairment (50–80 mL/min), moderate renal impairment (30–49 mL/min), and severe renal impairment (5–29 mL/min). A single 20 mg memantine dose was administered (under fasting conditions.) The study concluded that there were no relevant differences in maximum memantine plasma concentration between subjects with normal and impaired renal function (of any severity.) The mean area under the plasma concentration vs time curve extrapolated to infinity was similar between the groups of patients with normal and mildly impaired renal function, and it was increased by 60% (24–97%) in patients with moderate renal impairment and 115% (77–152%) in patients with severe renal impairment. Simulations predicted steady-state maximum concentration values of 82 ng/mL (70–95 ng/mL), 85 ng/mL (70–101 ng/mL), and 128 ng/mL in healthy people, those with mild renal impairment, and those with moderate renal impairment, respectively, for the recommended dosing regimen of 10 mg twice daily; for subjects with severe renal impairment, a steady-state maximum concentration value of 84 ng/mL was predicted for a dosing regimen of 5 mg twice daily. The study concluded that no dosage adjustments are needed for patients being treated with memantine 10 mg twice daily with mild or moderate renal impairment. However, target dose of 5 mg twice daily is recommended for patients with severe renal impairment [17].

Impaired Renal Function

Research with a randomized four-period crossover trial studied 12 healthy male volunteers receiving 10 mg memantine daily during 43 days. After reaching steady-state conditions, the volunteers were allocated to four different regimens to alter urine pH and urinary flow: acidified urine pH with low urinary flow (A regimen), acidified urine pH with high urinary flow (B regimen), alkalized urine pH with low urinary flow (C regimen), and alkalized urine pH with high urinary flow (D regimen). The renal clearance of memantine was higher in regimens A and B (with the probability value, i.e., the difference between the groups being $P < 0.05$). There were small but statistically significant differences of clearance between the two regimens with acidic urine pH (A—median of 210.2 mL min^{-1} vs B—median of 218.7 mL min^{-1}) and between the two regimens with alkaline urine pH (C regimen had a median of 19.4 mL min^{-1}, while D regimen had a median of 30.5 mL min^{-1}). The amount of memantine excreted into the urine within one regimen was 5.7–7.4-fold higher in regimens A and B than C and D ($P < 0.05$). Differences of the area under the curve (AUC) 0, 24 h and Cmax/AUC 0, 24 h were significant ($P < 0.05$) between each of the regimens with acidic urine pH (A and B regimens) and regimens with alkaline urine pH (C and D), i.e., A vs C, A vs D, B vs C, and B vs D, but not between regimens A vs B or C vs D. The study described has shown a considerable effect of urine pH in memantine, and no clinically relevant change of the renal excretion of memantine with the urinary flow could be detected. Since the renal excretion of memantine may have an impact on therapeutic efficacy of memantine, changes of dietary habits, intentional, by other reasons than memantine and that may alter urine pH, should be avoided during the treatment with memantine [18].

5.5.1.3 Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors, such as acetazolamide, dichlorphenamide, and methazolamide, reduce the enzyme carbonic anhydrase activity, which is responsible for catalyzing the reaction between carbon dioxide and water into carbonic acid and then into bicarbonate. That reduces the resorption of bicarbonate from the proximal tubule in the kidneys, causing a direct increase in bicarbonate excretion and mild increases in sodium and potassium excretion. Generally, the electrolyte effects of carbonic anhydrase inhibitors are mild, and they are typically not used for their diuretic capacity. Carbonic anhydrase inhibitors have an established place in the treatment of glaucoma. This role is based on over three decades of research on the anatomy and physiology of aqueous humor secretion, as well as the pharmacology and distribution of the sulfonamide carbonic anhydrase inhibitors in the eye, and this class of drugs decreases the secretion of aqueous humor (the clear fluid that fills the space between the lens and the cornea of the eyeball), resulting in a decreased intraocular pressure [6, 19, 20].

5.5.1.4 Sodium Bicarbonate

Sodium bicarbonate alkalinizes urine and may reduce renal elimination of memantine, increasing its effect and possibility of side effects and toxicity [5, 6].

5.5.1.5 Drugs Eliminated via Renal Mechanism

Memantine is eliminated in part by tubular secretion. In vivo studies have shown that multiple doses of hydrochlorothiazide/triamterene did not affect the AUC of memantine at the steady state. Memantine did not affect the bioavailability of triamterene, but it decreased the area under the curve (AUC) and maximum concentration (C_{max}) of hydrochlorothiazide by about 20% [7].

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Chapter 6
Supportive Pharmacological Treatment

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6.1 Antidepressants

Manifestations of depression are widely associated with psychiatric disorders in Alzheimer's disease (AD) that influence quality of life, ability to develop daily activities, cognition, and motor aspects. However, depression in AD is clearly underdiagnosed, and most patients do not receive specific treatment, with limitations in the progression of the disease and in aspects related to therapeutic prognosis [5].

The relation between depression and AD is still controversial because it is not clear whether depression is an independent risk factor for the disease or a nonspecific symptom in the elderly population. The deposition of cerebral β-amyloid peptide (Aβ) is associated with cognitive symptoms and neuropsychiatric symptoms (SPN), which can be a biological compensation mechanism. Despite the widespread use of antidepressant therapy, there is mixed evidence about the benefits of its use in AD depression. Monoaminergic antidepressants showed only moderate clinical benefits or no clinical benefits. Therefore, it is important to understand the reason for this drug resistance and the relation between antidepressants and the Aβ peptide [15, 27].

Symptoms are often accompanied by behavioral disorders, such as aggression, hallucinations, hyperactivity, irritability, and depression. Mood disorders affect a

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considerable percentage of individuals who develop AD at some point in the evolution of dementia. About 40–50% of patients have depressive symptoms, whereas depressive disorders affect around 10–20% of cases, mostly affecting the elderly population. Other symptoms such as apathy, slowness (gait or speech), difficulty concentrating, weight loss, insomnia, and agitation can occur as part of the dementia syndrome [15].

The clinical evidence proves to be sufficient for therapeutic indication; however, studies that evaluate the efficacy of antidepressant treatment in patients with AD are limited. Most of the published and studied data on this alternative therapy is based on individual experiences and extrapolations with depressed geriatric patients with no dementia. In this context, some of the symptoms can be confusing, which can hinder the therapeutic choice and cause potentially serious side effects [10].

Non-pharmacological interventions to alleviate depression in people with cognitive impairment and dementia include emotion-oriented therapies and behavioral, cognitive, and structured activity modification programs. Sensory stimulation therapies and multisensory approaches have shown benefits in the treatment of depression in patients with dementia, but more rigorous research is needed to establish its validity [8].

Clinical consensus and research show that selective serotonin reuptake inhibitors are the first choice for the pharmacological treatment of depression in patients with dementia. However, initial support for these therapies remains variable, and further investigation is needed. Increased care in the indication and prescription for this population is necessary due to the generally high level of comorbidities and psychiatric disorders and the potential difficulty in assessing the response of the patient with cognitive impairment [27].

In a systematic review and meta-analysis conducted with seven randomized, double-blind clinical trials, antidepressants such as sertraline, mirtazapine, fluoxetine, and clomipramine were compared with a placebo for depression in AD, noting that the statistically significant differences in drug-placebo for depressive symptoms were limited due to the low qualities of clinical trials [31]. In another research with published studies, it was shown that the heterogeneity in the way adverse events were presented in the research presented a great difficulty for the meta-analysis but presented some evidence that treatment with antidepressants causes more adverse effects than treatment with placebo [15].

Several antidepressants have been studied in the context of AD, but the interpretation of the clinical effects of the treatment is controversial due to the ambiguity of the results. Some studies are being conducted to determine whether antidepressants can be used as preventive agents of the disease, and not only prescribed in advanced stages, based on the hypothesis that these compounds treat not only neuropsychiatric symptoms but also to be able to reduce the production of Aβ [8].

Under these conditions, most of the available antidepressants have similar efficacy and response latency profiles. The choice of antidepressant depends much more on the tolerability profile (pharmacokinetics, side effects, potential for drug interactions), the associated clinical conditions (associated physical diseases, drugs prescribed concomitantly), the individual characteristics of the patient (past or

Table 6.1 Dosage schedule of the drugs most used in the treatment of depression in patients with AD

Medication	Usual therapeutic dose (mg/day)	Maximum dose under supervision (mg/day)	Restricted use
Fluoxetine	20–30	60	Parkinsonism and other extrapyramidal syndromes
Fluvoxamine	100–200	300	
Paroxetine	20–30	60	
Sertraline	50–100	200	
Citalopram	20–30	60	
Mirtazapine	15–45	45	Hypercholesterolemia
Trazodone	50–300	400	Apathy
Nefazodone	200	400	Psychomotor inhibition
Bupropion	150–300	450	Insomnia, psychomotor agitation, psychosis, and convulsions
Nortriptyline	50–125	150	Fecaloma
Moclobemide	150–600	800	Poor dietary supervision

Source: Forlenza [18, 19]; Sereniki and Vital [43]; Orgeta et al. [31]

family history of depression and AD), previous favorable response to a specific antidepressant, and the use of specific drugs for AD [5].

In special situations, the therapeutic potentials of new drugs such as bupropion, venlafaxine, and reboxetine must be considered or even traditional medicines, including tricyclic, tetracyclic antidepressants, and monoamine oxidase inhibitors. In addition, side effects should be considered; for example, patients who have prominent insomnia, psychomotor agitation, or aggressive behavior may benefit more from antidepressants with a sedative profile such as trazodone, mirtazapine, or tricyclic antidepressants. If, on the contrary, activation is desired in cases of depression with psychomotor inhibition or apathy, drugs such as SSRIs, bupropion, reboxetine, or desipramine should be preferred. Table 6.1 summarizes the dosing regimens of the most suitable drugs for the treatment of depression in patients with dementia [31].

In this perspective, advances in the development of new agents for cognitive and behavioral symptoms of AD with depression, combined with improved experimental methods, promise to meet the unmet needs of patients with AD to improve cognition and improve neuropsychiatric symptoms so that they can improve extension of cognition and the behavior of these diseases and the quality of life of patients [11].

6.2 Antipsychotics

6.2.1 Typical

Typical antipsychotics are the drugs used for the longest time in the treatment of behavioral syndromes and in the diagnosis of dementia, such as AD. As the main representative of this class, haloperidol is widely used in clinical practice, although

few controlled studies have been conducted. In 2008, a randomized, double-blind study was conducted: Haloperidol in doses of 2–3 mg/day was more effective than lower doses (from 0.5 to 0.75 mg/day) and than placebo in treatment of psychotic symptoms and psychomotor agitation [14]. However, another study showed greater side effects in the elderly, and haloperidol was also not superior to other typical antipsychotics in controlled studies, for example, trifluoperazine and thioridazine, with a higher incidence of extrapyramidal signs in the groups treated with haloperidol [21].

Antipsychotic doses in monotherapy were investigated in a study carried out with 920 users, in which 4% (n = 336) used high-dose antipsychotics during 2006–2009. Typical antipsychotics were used more frequently with high doses than atypical antipsychotics, which indicated the need for precise dosing instructions in the treatment of behavioral and psychological symptoms of dementia. The use of high doses was associated with younger age (<80 years) [45].

Regarding a selective serotonin reuptake inhibitor (SSRI), sertraline hydrochloride has shown positive results in contrast to other studies on the same drug and also with two other antidepressants: fluoxetine and citalopram [43]. In Europe, there is consensus on the indication of SSRI-based treatment, although this therapeutic recommendation is not supported by conclusive evidence as some clinical trials have shown beneficial effects on patients' mood.

In this perspective, the effects of SSRIs, which are commonly gastrointestinal changes (nausea, vomiting, and diarrhea), insomnia, restlessness, and, more rarely, hyponatremia should be considered. Sertraline and citalopram should be preferred because they have a shorter plasma half-life, little activity of their metabolites, low risk of drug interactions, and linear dose/response ratio [7, 18, 19].

Randomized, placebo-controlled, double-blind, and parallel group study involved 186 patients with AD and agitation in eight academic centers in the United States and Canada, from August 2009 to January 2013, using citalopram. Dosing started at 10 mg/day with a planned titration to 30 mg/day for 3 weeks based on response and tolerability. It was revealed that among patients with probable Alzheimer's disease and agitation who were receiving psychosocial intervention, the addition of citalopram compared to the placebo significantly reduced the caregiver's agitation and suffering. However, the adverse cognitive and cardiac effects of citalopram may limit its practical application at a dosage of 30 mg/day [34].

In a meta-analysis, it was shown that although some randomized clinical trials show SSRIs as the treatment currently most recommended for depression, others are ineffective in treating depressive symptoms in people with AD. One explanation for this lack of treatment effect may be that depressive symptoms may reflect the progression of AD rather than clinical depression and are a consequence of more severe neurodegeneration [16].

On the other hand, even in the absence of depression, SSRIs have been shown to delay the conversion of mild cognitive impairment to AD. This can be attributed to the effect of SSRIs on the processing of the precursor protein β-amyloid, which can cause a reduction in the accumulation of β-amyloid. Thus, although SSRIs may not be effective in treating depression in people with AD, they may have therapeutic

potential to treat and slow the progression of AD, especially if treatment begins in the early stages of AD [1, 7].

In order to quantitatively review published studies to examine the efficacy of the selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor for the relief of diagnosed comorbid depression, as well as cognitive decline in AD, it pointed out that there was no difference in five studies analyzed, in which they differed in terms of criteria for the diagnosis of depression, the compound tested, and outcome measures for depression, and these factors may explain the lack of a clear benefit for depression in AD [42].

Cholinesterases and monoamine oxidases are closely associated with symptoms and disease progression and have been treated simultaneously with the use of several multifunctional ligands. Several studies have indicated that monoamine oxidase inhibitors (MAOIs) improve cognitive deficits and reverse Aβ pathology, modulating the proteolytic cleavage of the amyloid precursor protein and decreasing Aβ protein fragments. Thus, MAO inhibitors can be considered promising therapeutic agents for AD [4, 26, 48].

MAOIs can be effective in treating patients with dementia since elevations of this enzyme activity have been described in affected patients. Medicines such as phenelzine and tranylcypromine have few anticholinergic properties, but their use should be indicated only in cases refractory to other options, due to the occurrence of postural hypotension (risk of falls and fractures) or hypertensive crises due to dietary failures [32]. Monitoring postural hypotension is essential, and caregivers must also supervise dietary restrictions and the use of other medications. Moclobemide, a reversible MAO-A inhibitor, eliminates the dietary restrictions of classic MAOIs and is generally well tolerated by the elderly. It presented a favorable profile of side effects and a response significantly superior to placebo in a sample of 694 patients with depression and cognitive decline, at an average dose of 400 mg/day [6].

In conclusion, it can be assumed that the use of typical antipsychotics is recommended for the treatment of depression in AD, but they should always be used in the lowest doses necessary to obtain the therapeutic benefits, being essential to take into account the non-pharmacological interventions adopted concomitantly. It should be noted that the monitoring of side effects must be cautious, especially with attention to excessive sedation and extrapyramidal manifestations.

6.2.2 Atypical

Second-generation antipsychotic drugs, also called atypicals, are widely used to treat psychosis, aggression, and agitation in patients with AD, but their benefits are uncertain and safety concerns have arisen. In addition, concerns have been raised about the increased risk of cerebrovascular adverse events, rapid cognitive decline, and mortality from its use [10].

Despite little scientific evidence, atypical antipsychotics may be associated with a small increase in the risk of death compared to placebo. This risk must be

considered in the context of the individual need for drugs, evidence of efficacy, comorbidity and efficacy, and safety of alternatives. Due to these factors, specific analyses of patients are needed to model survival and causes of death [36, 40].

In Italy, a retrospective population-based study showed that patients with dementia using antipsychotic drugs are at higher risk of death. This risk was greater for conventional prescribed antipsychotics. In addition, at least part of the excess mortality may be due to the underlying neuropsychiatric symptoms that led to the use of antipsychotics rather than the direct effect of the medication [30].

In a double-blind, placebo-controlled clinical trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg daily), quetiapine (mean dose, 56.5 mg/day), risperidone (medium dose, 1.0 mg/day), or placebo. Doses were adjusted as needed and patients were followed for up to 36 weeks. The study showed no significant differences between treatments with regard to the time to discontinue treatment for any reason, but improvement was seen in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo. In addition, the adverse effects outweigh the advantages in the effectiveness of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with AD [41].

The impact of atypical antipsychotics olanzapine, quetiapine, and risperidone on cognition in patients with Alzheimer's disease was measured in one study, showing that these drugs were associated with worsening cognitive function to a magnitude consistent with 1 year deterioration compared with placebo. Additional cognitive impairment is an additional risk of treatment with atypical antipsychotics, which should be considered when treating patients with Alzheimer's disease.

In a study carried out, patients with AD and sleep syndromes were treated with atypical antipsychotics (0.5–1 mg risperidone), non-benzodiazepine hypnotic (5–10 mg zolpidem tartrate), and melatonin (2.55 mg). The results showed that treatment with low-dose risperidone improved the outcome of 5 years in the patients evaluated. In addition, improving nighttime sleep problems in AD patients will also bring better emotional stability for caregivers with AD, including sleep, anxiety, and mood scales [47].

Trazodone is a predominantly serotonergic drug, with few anticholinergic effects, but with an important sedative action. In the absence of controlled clinical trials, some open studies support the use of trazodone in depressed patients with AD, with psychomotor agitation and sleep disorders (with or without depression) being the most frequent indications [18, 19].

There is also no record of controlled studies with bupropion in depressed patients with AD. It is an atypical antidepressant with predominantly dopaminergic action, devoid of anticholinergic, sedative, or cardiovascular effects. Although it provides a rapid onset of antidepressant action and psychomotor activation, it should not be used as a first option in patients at risk of convulsions as it may reduce the convulsion threshold. The most reported side effects are weight loss, anxiety, restlessness, and insomnia. Activation of the dopaminergic system can, in certain patients, induce or exacerbate psychotic symptoms [28].

Aripiprazole is a more recent atypical antipsychotic with partial agonist activity at dopamine receptors and antagonistic activity at 5-HT (2A) receptors, with a low profile of side effects. In placebo-controlled randomized clinical trials, aripiprazole shows modest efficacy in the treatment of AD-related psychosis. The relieved neuropsychiatric symptoms were predominantly psychotic and agitated. In individual studies, aripiprazole was generally well tolerated, and serious side effects were rarely reported and included accidental injury and drowsiness. In meta-analyses, however, they demonstrated increased mortality as a class effect for atypical antipsychotics as well as for typical antipsychotics. No increase in cardiovascular outcomes, strokes, increased appetite, or weight gain were demonstrated in meta-analyses for patients treated with aripiprazole with dementia psychosis [12, 39].

Thus, aripiprazole may have sedative effects and should only be used in selected populations of patients resistant to non-pharmacological treatment with persistent or severe psychotic symptoms and agitation, and in which the symptoms lead to significant morbidity, patient suffering, and potential self-harm. The indication of continuity of treatment should be regularly reviewed [39].

Although atypical antipsychotics are being used with increasing frequency, few randomized studies have evaluated their use for BPSD. Limited evidence supports the perception of better efficacy and adverse event profiles compared to typical antipsychotic drugs. Despite their current use, successive studies have shown that they confer only a modest benefit that must be balanced with their well-established serious side effects (extrapyramidal symptoms, stroke, accelerated cognitive decline, and mortality) [10].

6.3 Anxiolytics

The existence of anxiety disorders along with depressive disorders in individuals already diagnosed with AD contributes to the use of anxiolytics that can be maintained for long periods, increasing cases of dependence. Non-pharmacological treatment approaches have become the preferred first-line option. When this treatment fails, pharmacological options are often used. Therefore, there is an urgent need to identify effective and safe pharmacological treatments to efficiently treat agitation and aggression in AD, as well as dementia [25].

Benzodiazepines (BZDs) are drugs widely prescribed in clinical practice due to their anxiolytic, hypnotic, and muscle relaxant properties. However, its chronic use is associated with cases of abuse, dependence, and relapse in many patients. In addition, it is known that the elderly are susceptible to changes in pharmacodynamics and pharmacokinetics and also to drug interactions due to polypharmacy. These situations increase the risk for the appearance of cognitive disorders and the development of pathologies such as AD [48].

Studies have shown a vicious circle that worsens the condition of patients with AD on long-term use of BZD. These effects may be due to interference with the

usual GABA-A benzodiazepine or individual sensitivity to these drugs, especially in the elderly who may be more susceptible to these side effects. However, some research considers it possible that some individuals already had cortical evidence of mild cognitive impairment or impending AD before starting to take benzodiazepine although they did not have obvious clinical symptoms [3].

However, two other retrospective case-control studies have shown the opposite conclusion that the effect of benzodiazepines on cognition was small and not clinically significant [2, 22, 23]. Subsequent prospective population study also revealed no evidence of a causal association between the use of benzodiazepines and dementia [20]. Based on the review of these studies, authors have issued different opinions showing that the use of benzodiazepines does not cause dementia and can be widely used in the manifestations of agitation that can arise in AD [9, 38].

Thus, the preponderance of available data to date does not support a causal relationship between the low therapeutic use of benzodiazepines and the development of Alzheimer's or other dementias, despite the known impairment of mild and reversible memory associated with benzodiazepine doses that occurs in some individuals. Although approximately 80% of those with mild cognitive impairment do not progress to diagnosable dementia such as AD, anxiety about memory decline is common ("old age") and can interfere with quality of life and sleep [37].

In the elderly, mild cognitive impairment can also be treated with low-dose benzodiazepines to improve daytime calming (as well as sleep onset), and this use may be beneficial. It is interesting to highlight the possible neuroprotective effect of benzodiazepines as individuals age, despite the small and generally reversible neurocognitive side effects. Anxiety can be a marker of prodromal AD in patients with mild cognitive impairment. Anxiety is said to be greater in early-onset AD than in late-onset AD, especially in men [35]. It is conceivable, therefore, that the calming effect, in addition to the hypnotic effect of sleep onset and the use of low doses of benzodiazepines in elderly people with anxiety, can reduce the effects of stress on CNS aging and reduce the risk of vulnerability to development by AD [24, 25].

Clinical trials on the effect of benzodiazepines on cognitive functions, AD progression, behavioral symptoms, sleep disorders, and the general frequency of benzodiazepine use were included in a systematic review. The frequency of use of benzodiazepines varied from 8.5% to 20% in the studies analyzed. Five studies reported accelerated cognitive impairment in association with the use of benzodiazepines. Two studies reported clinical efficacy for lorazepam and alprazolam to reduce agitation in patients with Alzheimer's disease, and thus, no evidence was found for improving sleep quality with the use of benzodiazepines [13].

Clonazepam is highly effective in the treatment of nocturnal behaviors associated with behavioral disorder of rapid eye movement. For most patients with dementia, however, the risks of side effects from prolonged use of sedatives should be weighed against the potential benefits. Dementia patients should be evaluated for common primary sleep disorders that can contribute to nocturnal behavioral disorders and affect treatment decisions. Continuous positive airway pressure—the gold standard for the treatment of obstructive sleep apnea—can be tolerated by individuals with mild to moderate dementia, with the support of supervisory caregivers [29].

Research that aimed to clarify the differential acute cognitive impact of lorazepam based on the variable genetic risk for AD showed that after the use of 6 months of lorazepam, there were significant declines from baseline in memory, psychomotor processing speed, and executive function [44]. In another study, low doses of diazepam (0.05 mg/kg) were shown to be effective, preventing neuroinflammation, preserving synaptic plasticity, as well as normalizing protein expression in the hippocampus and cortical related to acetylcholine breakdown and GABA biosynthesis. Thus, it was suggested that in low doses, diazepam targets nonspecific GABA-A, probably allosteric receptor sites, leading to stimulating effects that may be beneficial for use in the early stages of pre-dementia AD [33].

Due to limitations, there is little doubt that benzodiazepines, like other hypnotic sedatives, may be associated with impaired and generally mild cognition in a dose-dependent manner. The usual recommendations are to use only short half-life benzodiazepines in low doses and, if clinically possible, for short periods of time. Still, it emphasizes the need for individual assessment of some individuals, in which they may refer to reduced short-term memory in exchange for a calmer day and a reliable beginning of sleep. Future studies are needed on the possible associations of benzodiazepines (and other drugs) with the development of cognitive disorders in old age. Until then, we must assume that the proper use of benzodiazepines will not lead to the development of AD [13, 25].

6.4 Mood Stabilizers

Psychiatric drugs belonging to the class of mood stabilizers are used in the treatment of mood disorders of the intense and frequent type, such as bipolar and schizophrenic disorders [76]. Patients with Alzheimer's or dementia, who experience agitation and extreme mood swings, use mood-stabilizing drugs, such as valproic acid, lamotrigine, and lithium [53].

Lithium is one of the drugs used in the treatment of bipolar disorder for more than 50 years. It is known that this drug acts in several systems of neurotransmitters and mechanisms of signal transduction: hydrolysis of phosphoinositol, adenyl cyclase, protein G, GSK-38β, and protein kinase C [52].

Important pathological processes of Alzheimer's disease can be inhibited by lithium, including the overproduction of insoluble β-amyloid (βA) and hyperphosphorylation of tau. And these are the two main brain injuries found in patients with Alzheimer's disease, in addition to preventing memory impairment, a process induced by βA. Thus, these effects generate progress in the damage caused to memory [65, 71].

Cheng et al. [52] found that there are several studies in vitro and in vivo which reveal the neurotrophic and neuroprotective effects of lithium. The action of such a drug in practically all neurotransmitters allows the adjustment of the balance between excitation and inhibition as well as attenuation of the activity of the neurotransmitter glutamate. However, periodic control of this drug is essential in view

of the potential to cause exacerbation of cognitive impairments and increased tremors, in addition to interacting with other drugs, including diuretics, thiazides, calcium antagonists, and nonsteroidal anti-inflammatory drugs [73].

Elderly people with Alzheimer's disease should use lower doses, preferably one-third or half of the adult's usual lithium dose and, thus, obtain blood therapeutic levels around 0.5–0.8 mM/l. A study that evaluated the safety and viability of lithium in elderly patients demonstrated that this drug has few side effects; however, it was not conclusive to exempt problems related to this drug [67].

The drugs carbamazepine and valproic acid, although anticonvulsants, are used as mood modifiers. These drugs can be used in the face of agitated behaviors. They are well-tolerated drugs and produce minimal cases of toxicity, being therapeutic options for treating symptoms of Alzheimer's disease. The most studied drugs are carbamazepine at a dose of 200–800 mg/day and valproic acid at a dose of 250–1000 mg/day [56]. Valproic acid has been shown to be effective in the treatment of behavioral disorders in dementia, in addition to having less drug interaction when compared to carbamazepine [79].

A randomized study with 51 elderly patients with Alzheimer's disease, who presented symptoms of agitation, demonstrated that the drug carbamazepine with a daily dose of 300 mg was significantly effective in controlling such symptoms. Furthermore, the medication was well tolerated and safe [78].

Randomized placebo-controlled study, lasting 6 months, developed by Porsteinsson et al. [72], found that patients using valproic acid at doses of 840 mg daily showed improvement according to the agitation subscale of the Brief Psychiatric Assessment Scale (BPRS). The participants were elderly and lived in homes, presenting symptoms such as dementia and agitation [55, 72].

Even with the possibility of using carbamazepine and valproic acid in Alzheimer's disease, these medications are also more complicated to handle in the elderly population since in this population, the amount of serum albumin-like protein is reduced and, consequently, the drug fraction free is greater, which can lead to serious adverse reactions [69].

6.5 Vitamins

The high consumption of oxygen and the highly lipid environment provide the brain with vulnerability to damage, and the formation of reactive oxygen species causes neuron degeneration. Antioxidant nutrients such as vitamin E and vitamin C help in neutralizing the processes of lipid peroxidation, apoptosis, and protein damage. A study developed with rats in 2002 proposed evidence of improvement in cognitive function during aging, as a consequence of supplementation of high vitamin E intakes [57].

Vitamin E (alpha-tocopherol) is a group formed by eight compounds of lipophilic character, which interact not only with cell membranes but also capture free radicals having antioxidant activity [50]. In research with animal models, alpha-tocopherol decreased the degeneration of cells in the hippocampus and increased the rehabilitation of motor function after spinal cord injury. In cultures of hypoxic neurons, this same substance inhibited lipid peroxidation and decreased cell death related to the β-amyloid protein [62].

A systematic review carried out recently concluded that the use of vitamin E in Alzheimer's disease was insufficient. This conclusion was confirmed by the study by [17], which observed a slight increase in mortality in patients who received doses higher than 4000 IU/day, not recommending the use of such substance [17, 68].

Gugliandolo et al. [61] showed in their research that α-tocopherol modulated the expression of the genes involved in autophagy and the cell cycle, both known to be altered in AD. In that study, treatment with α-tocopherol was also able to reduce oxidative stress, restoring nuclear factor derived from erythroid 2-like 2 (Nrf2) and decreasing levels of inducible nitric oxide synthase (iNOS), as demonstrated by immunocytochemistry.

6.6 Antioxidants

The oxidative mechanism can directly influence neurodegenerative diseases such as Alzheimer's disease and processes associated with cell aging. Therefore, the use of antioxidant substances in the treatment of Alzheimer's disease is based on scientific evidence that reports the formation of oxygen free radicals in the pathogenesis of this disease by decreasing the cell aging process [60, 68].

One of the substances that can have positive effects in patients with Alzheimer's disease is selegiline—a monoamine oxidase inhibitor drug that acts as an antioxidant agent—because it inhibits oxidative deamination, decreasing neural damage. This inhibitor also increases the amount of catecholamine levels and the stimulation of the adrenergic response, consequently improving the cognitive deficits associated with Alzheimer's disease [51, 59].

The research by Sanders and Rajagopal [74] determined the delay of the drug selegiline in the clinical deterioration associated with Alzheimer's disease. The use of the drug proved to be beneficial in delaying the progression of the disease, and the results of this study suggested an improvement in the functionality of neurons or an increase in the survival of such cells by inhibiting oxidative deamination. Thus, the role of this drug in the treatment of this disease is of great interest, but the effectiveness remains questionable, reflecting the low amount of prescriptions and the disapproval of several regulatory authorities in several countries.

6.7 Secondary Treatment

Statins
Despite not having a solid scientific basis to date to be used in Alzheimer's disease, statins have shown in studies the ability to influence cholesterol levels in the amyloid metabolic pathway. Moreover, no significant benefit was associated with atorvastatin 80 mg/day therapy for the treatment of dementia in Alzheimer's disease [58].

Estrogen
In view of the physiological effects and epidemiological data, the possibility of favorable use of estrogen in the treatment of Alzheimer's disease arose. Estrogen-based therapy has been suggested as a way of preventing cognitive impairment in postmenopausal women. Such substance causes effects on the brain region and is responsible, among others, for the process of activating growth factors and increasing blood supply in the brain region [56, 63, 68].

Although initial studies suggested that hormone replacement could have positive effects on cognition, this was true for a small number of participants. These data were not confirmed in randomized studies that had a greater participation of patients. There has been no clinical evidence for its indication so far; however, the risk of developing side effects is great [63].

Ginkgo Biloba
The extract of ginkgo biloba (EGb761) consists of bioactive molecules capable of promoting an increase in blood supply to the brain region. This process is a consequence of vasodilation and reduced blood viscosity. These assets are also responsible for the reduction of free radicals in the nervous tissue. Laboratory models suggest that such compounds cause protection that prevents oxidative damage. However, its cellular and molecular mechanisms of action are still not fully understood [70].

Anti-inflammatories
The inflammatory reactions that occur in the amyloid plaques enable the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in an attempt to help prevent Alzheimer's disease, which may have a neuroprotective effect. Although old studies indicate no association with reducing the risk of dementia, the study developed by Forlenza [59] observed that the prolonged use of these drugs would be linked to a small reduction in the incidence of this disease. This fact is restricted to individuals who make chronic use of anti-inflammatory drugs, as in the case of patients with rheumatic diseases [59, 64].

The multicenter randomized, double-blind clinical trial found that medications such as low doses of rofecoxib and naproxen did not prevent the clinical progression of the disease in patients with mild to moderate Alzheimer's disease. The number of side effects, specifically gastrointestinal bleeding and cardiovascular risks linked to use, limits the prescription [49].

Neuronal Growth Factor

The neuronal growth factor (NGF) has been proposed as a treatment strategy for Alzheimer's disease since the neurons of the cholinergic nuclei of the basal forebrain are sensitive to this factor. Intravascular administration of NGF was performed in three patients with this disease, resulting in improved cerebral blood flow patterns. However, relevant side effects suspended the study and made it impossible to present and validate the data [66, 77].

Antiamyloid Therapy

Antiamyloid therapy is based on the amyloid cascade hypothesis, based on the pathological evidence of Alzheimer's disease. This treatment model reports that neurodegeneration in this disease begins with the breakdown of the amyloid precursor protein (PPA), ending in a routine process of accumulation, aggregation, and deposition of toxic forms of the beta-amyloid substance, which marks the beginning of the Alzheimer's process. Fibrillogenesis inhibitors, formation inhibitors, and clearance promoters are examples of categories of drugs with antiamyloid properties. Several studies conducted with these types of therapies show that these options can assist in the treatment of patients with such a disease but are still in experimental stages [54, 75].

Other Drugs

Melatonin, vasodilators, calcium channel blockers, and nootropics are substances that have, in common, supposed action on the central nervous system and are constantly prescribed despite not having demonstrated effectiveness in scientific studies. Therefore, they should not be used as a therapy option [59].

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Chapter 7
Herbal Medicines and Supplements

Eduardo Carità

Abbreviations

AD	Alzheimer's disease
ApoE	Apolipoprotein E
BBB	Blood-brain barrier
GpP	P-Glycoprotein
LD50	50% lethal dose
LDC	Lipid drug conjugates
LNCs	Lipid nanocapsules
LPRs	Low-density lipoprotein receptor-related proteins
NLC	Nanostructured lipid carriers
NLs	Lipid nanoparticles
NPs	Nanoparticles
PBCA	Poly(n-butylcyanoacrylate)
PEG	Polyethylene glycol
SLNs	Solid lipid nanoparticles
TCM	Traditional Chinese medicine
TEER	Transendothelial electrical resistance

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7.1 Introduction

With the advance of longevity, thanks to resources such as water and sewage and vaccines and antibiotics, just to mention the most striking, the growing prevalence of neurodegenerative diseases, together with the set of so-called civilizational diseases, became evident. We live longer, and, therefore, the usage time of the neural apparatus is prolonged. Differentiated in embryology, starting from the neural ectoderm in the beginning, we spent 50 or 60 years using and abusing this complex histological system until, eventually, we started to show signs of malfunction. Alzheimer's disease emerges as an important candidate for the epidemiological concerns of the twenty-first century, with significant advances in diagnostic methods but with a relative gap in therapeutic methods. Thus, we observe, intrigued, the increase in the number of cases of Alzheimer's disease (AD). Dear family members slowly go from loving and happy living together to the stage of memory loss, to the point where they do not recognize their closest relatives. Then they lose their identity and irreparably disrupt the delicate universe of feelings. The consequences of Alzheimer's disease are accentuated daily, interfering with the harmonious coexistence of family and friends. Currently, the search for a possible cause, or for the causes that lead to neurodegeneration, has become a trend, which has caught the attention of researchers from the most diverse fields of Life Sciences. However, we can consider this area from an even broader perspective, based on the knowledge of the ancestors of Ayurvedic and Chinese medicine about the therapeutic and biological properties, especially of plants, but with a modern perspective that allows us to define with more precision, which are its bioactive molecules, until we reach modern herbal medicine. Thus, we work with the aim of recovering traditional secular knowledge that was forgotten or lost with the evolution of science. In fact, the plants that have been used and studied for centuries, especially in recent years, will be listed here, as widely as possible, in an attempt to design an ethnopharmagnostic panel, based on their biochemical and phytochemical bases, that are relevant to the prevention and control of Alzheimer's disease. With the advent of increasingly earlier diagnostic methods, there is a great gap between the moment of awareness of having AD, the onset of clinical symptoms, and the beginning of treatment to effectively attack the causes of the disease, often at a remarkable advance. If it is still impossible to talk about total control, a well-founded process for slowing down the frame is part of our proposal. In this context, herbal supplements derived from the most advanced technology applied to time-honored bioactive molecules play a fundamental role, especially when supported by the possibilities arising from nanotechnology applied to this ancestral knowledge, ethnopharmagnostic phytotherapy, that is, the stabilization and delivery of actives in a much more efficient and targeted way, enabling the perfect balance and union between the traditional knowledge of the past and the present, connecting with the future. In short, in this work, we are inspired by this perspective of developing new and effective weapons, in this war for the preservation of mental health and for the integrity of what is most dear and valuable, our identity, our self.

7.2 Traditional Proposals of Indian Medicine

The precise translation of the ancestral Ayurvedic concept to Western medicine is a great challenge. Life Sciences are shaped by the philosophy of each civilization and strongly influenced by culture, customs, and ways of understanding the cause, purpose, and destiny of life itself. However, the influence/interpenetration of Eastern and Western culture grows more and more, with the increasing practice of Yoga and transcendental meditation and the spread of religions and even of cuisine, coming from the East. This has made it easier to rationally understand these medicinal practices, which have been so successful and consolidated over time. The physiological and biochemical constituents of man are always the same, except for small genetic subtleties and the intervening action of epigenetic factors, which will configure varied phenotypes. They are repeated to exhaustion, in the construction of our species, proteins, fats, and sugars, subsisting in an infinite myriad of sizes, colors, shapes, and characteristics, to finally take shape in different cultures and civilizations.

Time and the empirical application of old formulas refreshed by new "insights" allow us to advance and structure new control strategies for ancestral diseases that can be proven, such as in the case of dementia. Going back to the beginning of human existence, Ayurvedic medicine is one of the oldest documented systems of holistic ("whole body") healing in the world, and this is very relevant and important.

It began to be developed over 3000 years ago in India. It is based on the belief that health and well-being depend on a delicate balance between mind, body, and spirit. The restoration of mental health depended on the spiritual, psychic, and rational planes, as well as the physical. Thus, their rituals ranged from prayers and hymns, repetitive reading of codes of conduct, meditation, concentration, analytical self-knowledge, and self-confidence to restore mental balance. Drinks, oils, and ointments were spread over the head and body, sprayed through the nose, soaked in bandages, and even soaking the whole body in these substances, in order to prolong their effects.

The three tables, Tables 7.1, 7.2, and 7.3, provide indicative information with the original Ayurvedic name, its scientific name, its popular name, the parts commonly used, and its assets and possible mechanisms of action. The second, in particular, contemplates the multicausal and polysymptomatic view of dementia in its various variants, associating plants, extracts, and compounds aiming at their combined, synergistic action. For example, Table 7.1 lists plants such as *Glycyrrhiza glabra*, *Convolvulus*, *Centella asiatica*, *Crocus sativus*, *Bacopa monniera*, *Withania somnifera*, and *Curcuma longa*, all specimens recently studied in clinical trials, in isolation or associated with allopathic medication [95].

Stand out in Table 7.1: *Glycyrrhiza glabra*, *Convolvulus*, *Centella asiatica*, *Crocus sativus*, *Bacopa monniera*, *Withania somnifera*, and *Curcuma longa*, all specimens recently studied in clinical trials, isolated or associated with allopathic medication.

The scientific and cultural integration is presented from the perspective of the historical condition of the time, proving the trilogy body, mind, and spirit, guiding

Table 7.1 Ayurvedic herbs used in isolation, important in AD (alphabetical order)

Ayurvedic herb.	Scientific name	Common name	Part used	Active constituents	Possible mechanism of action	References
Amalaki	*Emblica officinalis* (Phyllanthaceae)	Amla, Indian gooseberry	Fruit	Tannins, phyllembelin, pectins, vitamin C	Antioxidant, improves amnesia and memory deficits	Vasudevan M (2007) [110]
Aparajita	*Clitoria ternatea* (Leguminosae)	Blue pea, butterfly pea	Root/root bark	Inositol, cyclohexen, 1-methyl-4-(1-methylethylidene)	Increases levels of ACh, nootropic	Rai (2005) [84]
Ardraka	*Zingiber officinale* (Zingiberaceae)	Zinger rhizome	Root	Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone)	Improves recall, retention, and acquisition	Gharibi et al. (2014) [36]
Ashwagandha	*Withania somnifera* (Solanaceae)	Indian ginseng, poison gooseberry, or winter cherry	Roots	Sitoindoside IX, sitoindoside X, withanolides, withanols	Anti-inflammatory, antioxidant, Aβ inhibition, AChE inhibition. Regenerates damaged axons, dendrites, and synapses	Kulkarni and Dhir [60]
Brahmi	*Bacopa monniera* (Scrophulariaceae)	Brahmí, water hyssop, Indian pennywort	Leaves, roots	Bacoside A	Antioxidant, nootropic, cognitive enhancer	Singh and Dhawan [97]
Dadima	*Punica granatum* (Punicaceae)	Pomegranate	Flower, fruits	Anthocyanin compounds	Neuroprotective, antioxidant, improve learning abilities and memory retention	Cambay et al. [14]
Dhanyaka	*Coriandrum sativum* (Apiaceae)	Coriander	Seed	2-Decenoic acid, E-11-tetradecenoic acid, capric acid	Antioxidant, anti-inflammatory, anticholesterolemic, improves amnesia	Vasudevan and Parle (2009) [109]

Phalgu	*Ficus carica* (Moraceae)	Common fig	Fruit	Anthocyanin composition, triterpenoids, coumarins	Antioxidant, improves amnesia, nootropic	Saxena et al. (2013) [92]
Guduchi	*Tinospora cordifolia* (Menispermaceae)	Giloy	Stem	Tinosporine, tinosporide, giloin, magnoflorine	Antioxidant, antipsychotic, neuroprotective, nootropic, ACh synthesis	Sharma et al. [94]
Guggulu	*Commiphora whighitii* (Burseraceae)	Guggul	Resin	Guggulsterones, manusumbionic acid	Antidementia, AChE inhibition, nootropic	Gujuran et al. [41]
Haridra	*Curcuma longa* (Liliaceae)	Common turmeric	Rhizome or root	Curcumin	Anti-amyloidogenic, anti-inflammatory, anti-ChE, anti-β-secretase	Rajakrishnan et al. [85]
Jatamansi	*Nardostachys jatamansi* (Valerianaceae)	Spikenard	Dried rhizomes, roots	Gallic acid, catechin, chlorogenic acid, homovanillin, epicatechin, rutin hydrate, and quercetin-3-rhamnoside	Improves stress-induced memory deficit and amnesia	Karkada et al. [53]
Jatiphala	*Myristica fragrans* (Myristicaceae)	Nutmeg	Seed	Camphene, beta-pinene, sabinene, cymene, geraniol, d-borneol, linalool, terpineol	Improves learning and memory deficits	Parle et al. [77]
Jyotishmati	*Celastrus paniculatus* (Celastraceae)	Black oil plant, climbing staff tree, and intellect tree	Seed oil	Talsaclidine	Neuroprotective, antioxidant, improves ACh levels	Bhanumathy et al. [9]
Kumkum	*Crocus sativus* (Liliaceae)	Saffron	Dried stigma	Safranal	Inhibits impairment of hippocampal synaptic plasticity and fibrillogenesis	Papandreou et al. [76]
Kushmanda	*Benincasa hispida* (Cucurbitaceae)	White gourd	Fruit	Triterpenes, sterols, and glycosides	Antipsychotic, neuroprotective, antioxidant, nootropic	Roy and Ghoush [90]

(continued)

Table 7.1 (continued)

Ayurvedic herb.	Scientific name	Common name	Part used	Active constituents	Possible mechanism of action	References
Mandukaparni	*Centella asiatica* (Apiaceae)	Brahmi, Asiatic pennywort or Gotu kola	Leaves, roots	Asiaticoside, oxyasiaticoside, centelloside, brahmoside, brahminoside	Antioxidant, AChE inhibition	Kumar and Gupta (2002) [62]
Nithya Kalyani	*Catharanthus roseus* (Apocynaceae)	Sadabahar, red periwinkle	Dried roots	Ajmalicine, dimeric, vinblastine, vincristine	Neuroprotective, antioxidant effect	Jyothi P and Kumara SD (2012) [51]
Patha	*Cissampelos pareira* (Menispermaceae)	Velvet leaf	Whole vine	Hayatine, hayatidine, berberine	AChE inhibition, antioxidant, anti-inflammatory	Pramodinee et al. [82]
Puga	*Areca catechu* (Arecaceae)	Areca nut, betel nut, areca nut palm, betel palm	Fruit	Arecaidine, arecoline, guvacine	Inhibition of MAO-A, muscarinic (M2) binding activity	Houghton and Seth [44]
Shalparni	*Desmodium gangeticum* (Fabaceae)	Sal. leaved desmodium	Root	Pterocarpan, pterocarpanoids gangetin, gangetinin, desmodin	AChE inhibition, nootropic	Joshi and Parle [48, 49]
Shankhapushpi	*Convolvulus pluricaulis* (Convolvulaceae)	Morning glory, bindweed	Whole plant	Triterpenoids, flavanol glycosides, anthocyanins	Antidementia, AChE inhibition, nootropic	Amin et al. [5, 6]
Shatavari	*Asparagus racemosus* (Liliaceae)	Water roof, wild carrot, Shatavari	Fresh tuber	Asparagine, shatavarin	Antioxidant, inhibiting MAO-A and MAO-B	Dhingra and Kumar [22]

Shigru	*Moringa oleífera* (Moringaceae)	Drumstick plant	Leaf	9-Octadecenoic acid	Antioxidant; modify levels of monoamines such as norepinephrine, dopamine, and serotonin	Obulesu and Rao [73]
Shati	*Salvia lavandulifolia* (Lamiaceae)	Sage weed	Extracted essential oil	1,8-Cineole, α-pinene, β-pinene	AChE inhibition	Perry et al. [81]
Vacha	*Acorus calamus* (Araceae)	Sweet flag	Rhizome	β-Asarone, α-asarone	Sedative, neuroprotective, nootropic	Vohora et al. [111]
Yashtimadhu	*Glycyrrhiza glabra* (Fabaceae)	Licorice	Root	Glycyrrhizin, 2,2′,4′-trihydroxychalcone	Neuroprotective, anti-inflammatory, antioxidant, nootropic, antidementia	Chakravarthi and Avadhani [15]

Adapted from source: Sharma et al. [95]

Ayurvedic medicinal practices, which persists in that culture until the present times, which can be seen in Table 7.2.

On the other hand, a sample of India's cultural heritage, which has increasingly influenced Western culture and even medical practices today, coming out of the laboratory benches and presenting itself as a supporting in association formulas, or even a protagonist, being the object of several studies, with statistical significance of efficacy, in clinics and hospitals around the world, is shown in Table 7.3.

Table 7.2 Ayurvedic poly-herbal formulations used in dementia and neurodegeneration (alphabetical order)

Formulation type	Formulation name	Description of traditional usage
Arka (*distillates*)	*Shankhakeetadi Nasya*	Used as nasal drops in mental disorders
Asava/Arishta (fermentative drinks)	Saraswatarishta	Various mental disorders, dementia, mental weakness
Avaleha	*Chandravleha*	Mental weaknesses
Bhasma (calcium and mineral preparations)	*Mukta Pishti*	For mental disorders with Pitaya involvement
	Rajata Bhasma	Weak memory
	Swarna Bhasma	Weak memory
	Smritisagara Rasa	Various mental disorders
	jyotishmati rasayana	Promotion of intellect

Consultation source adapted from: Sharma et al. [95]

Table 7.3 Traditional Ayurvedic plants and their phytoconstituents effective in AD

Plant source	Phytoconstituent	Traditional use	AD drug target	References
Bacopa monniera	Bogenines, steroids, triterpene	Ayurvedic medicine; improve intelligence and memory	Ameliorates ACh deficits in vivo	Uabundit et al. [106]
Cassia obtusifolia	Obtusifolin	Eastern medicine; used as a topical analgesic and anti-inflammatory natural medicine	AChE inhibition	Kim et al. [56]
Centella asiatica	Triterpene glycosides, saponins	Ayurveda; anxiolytic agent and cerebral tonic	Reducing Aβ in vivo	Dhanasekaran et al. [21]

Table 7.3 (continued)

Plant source	Phytoconstituent	Traditional use	AD drug target	References
*Crocus sativus**	Carotenoids and others	Mediterranean, Asia; to treat all varieties of gastrointestinal ailments	Clinical trial	Akhondzadeh et al. [3]
Desmodium gangeticum	Aminoglucosyl glycerolipids, cerebrosides	Ayurveda; treatment of neurological disorders	Reserved amnesia, AChE inhibition	Joshi and Parle [48]
Kami-kihi-to *Astragalus* root, *Bupleurum* root, *Atractylodes lancea* rhizome, ginseng root, *Hoelen* and *Polygala* root, gardenia fruit, jujube fruit, Japanese angelica root, *Glycyrrhiza* root, ginger rhizome, *Saussurea* root, *Ziziphus* root, longan fruit	Composition of 12 crude drug herbs	Kampo; to treat neurosis, amnesia, and anemia	Aβ toxicity in vivo: neuritic, synaptic, and myelin losses	Tohda et al. [104]
Murraya koenigii Indian curry leaf	Carbazole alkaloids, Scoponin	Indian flavor	Anti-amnestic, reduced ChE activity	Vasudevan and Parle [109]
Yokukansan *Atractylodes lancea* rhizome, *Poria* sclerotium, *Cnidium* rhizome, Japanese *angelica* radix, *Bupleurum* radix, *Glycyrrhiza* radix, and *Uncaria* thorn	Composition of four crude drug herbs	Kampo; to treat restless leg syndrome and agitation in children	Aβ toxicity in vivo: decrease in the anxiety, increase in locomotor activity in Tg2576 AD mice	Tabuchi et al. [102]
Zokumei-to *Prunus armeniaca* L., *Ephedra sinica Stapf* STAPF, *Cinnamomum cassia Blume*, *Panax ginseng* C.A. MEYER, *Angelica acutiloba* KITAGAWA, *Cnidium officinale* MAKINO, *Zingiber officinale* ROSCOE, *Glycyrrhiza uralensis* FISCH, and *Gypsum fibrosum* (gypsum)	Composition of different crude drug herbs	Kampo; to treat post-apoplectic sequelae	Aβ toxicity in vivo; increase in synaptophysin levels, abolishes neuronal loss	Tohda et al. [104]

Consultation source adapted from: Sharma et al. [95]

7.3 Proposals of Traditional Chinese Medicine

Acupuncture, moxibustion, massage, and herbal medicine are the main constituent parts of traditional Chinese medicine. Although acupuncture is well known in many Western countries, Chinese herbal medicine, the most important part of traditional Chinese medicine, is less well known in the West. Table 7.4 cites the main representatives of this important branch of medical knowledge, with examples of how medicines derived from Chinese herbs were developed from traditional therapeutic experience. One can clearly see some examples that ended up arriving in the West, today, being incorporated and influencing modern Western herbal medicine. Natural products, mainly of plant origin, represent sources of compounds with potential therapeutic implications in AD and other cognitive dysfunctions. Drug discovery from medicinal plants has traditionally been a long and more complicated process than other forms of innovation development. The selection of bioassays from plant extract libraries faces significant difficulties. On the other hand, the discovery of new compounds is a crucial strategy for the development of new drugs. By recalling the pathogenesis of AD, we try to give a broader view on the identification of compounds and the development of new drugs, in order to rationalize the design of drugs with better results and therapeutic benefits. Considering the multi-target strategy as the cause of AD, the synergistic use of herbal medicines with conventional

Table 7.4 Overview of plants and their active compounds useful in diseases of the nervous system originating from TCM

Plant source	Phytoconstituent	Traditional use	AD drug target	References
Danggui-Shaoyao-San./*Angelica* sinensis (Oliv.) Diels, *Ligusticum chuanxiong* Hort, *Paeonia lactiflora* Pall., *Poria cocos* (Schw.) Wolf, *Atractylodes macrocephala Koidz.*, and *Alisma orientalis* (Sam.) Juzep.	Extract/mixture of medicinal herbs	TCM, TJM; enhancement of women's health	Apoptosis in vitro	Qian et al. [83]
Dipsacus asper	Akebia saponin D	TCM; enhancing kidney function	Aβ toxicity	Zhou et al. [122]
Fungi *Monascus purpureus*	*Monascus*-fermented red rice	TCM; enhancement of blood flow	AChE activity, antioxidant, secretase activity	Lee et al. [64]

Table 7.4 (continued)

Plant source	Phytoconstituent	Traditional use	AD drug target	References
Fungus Ganoderma lucidum	Ganoderic acid (triterpene glycosides)	TCM; as antitumor, immunomodulatory, and immunotherapeutic agent	Preserving synaptic density, preserving Aβ-induced apoptosis	Lai et al. [63]
Ginkgo biloba	Fresh plant extract	TCM; for respiratory disorders, improve memory loss	DemTect cognition score	Bäurle et al. [7]
Lycium barbarum	Polysaccharides	TCM; used as antitumor, immunomodulatory, and anti-hypertension agent	Reverses Aβ and homocysteine-induced apoptosis	Yu et al. [118]
Ginseng	Leaf and root	TCM; antioxidant, anti-amyloidogenic, anti-apoptotic	Secretase	Chen W et al. [17]
Paeonia suffruticosa	1, 2, 3, 4, 6-penta-o-galloyl-d-glucopyranose	TCM; to treat inflammatory and pyretic disorders	Aβ formation, stabilization; in vivo long-term memory impairment	Fujiwara et al. [32]
Panax ginseng (Burkill)	Ginsenoside Rg1	TCM; improving learning and memory function, cholinergic neuron protector	Secretase activity	Cheng et al. [18]
Panax notoginseng	Ginsenoside	TCM; improving learning and memory function	Neprilysin	Yang et al. [115]
Polygala tenuifolia	Tenuifolin (extract)	TCM; to improve memory loss	Secretase activity; morphological plasticity	Lv et al. [67]
Qiong Yu Gao (Poria Cocos (Fuling), Ginseng Radix et Rhizome (Renshen) and MEL (Baimi), *Rehmannia glutinosa Libosch.*	Catalpol, rehmaglutin A, rehmaglutin B, rehmaglutin D, adenosine, acteoside, daucosterol, echinacoside, martynoside, rehmaionoside B, and rehmaionoside C	TCM; to treat AD by multi-target active compounds	Adenylate cyclase-inhibiting G-protein-coupled acetylcholine receptor signaling pathway	You et al. [116]

Adapted from source: Sharma et al. [95]

pharmacotherapy, already widely used in traditional medicine in AD, provides an unexplored source of therapies. Traditionally applied herbal preparations offer adjuvant therapy to drugs that act on the genesis of amyloid.

The reasons behind these few approvals seem to be the complex nature of the chemical components in herbal preparations in addition to the difficulties of standardization. The identification of medicinal herb assets will significantly increase the acceptance of these medicinal plants in clinical practice, as in vitro, in vivo, and clinical trials advance. In fact, some human studies have confirmed the beneficial effects of herbal medicines in preventing and treating dementia [31, 79, 80, 113]. Based on the encouraging results of animal studies and the proven safety over time of some of the herbal agents, the use of these agents as adjuvant therapy, along with conventional drugs, may be suggested. The therapeutic effects of most herbal medicines are increasingly being confirmed in academic settings [40].

In the Table 7.4, there is a small summary of the main vegetable sources of traditional use in Chinese medicine, their main active components, their customary use, and their pharmacological targets.

The highlights are *Panax ginseng* and Qiong Yu Gao, which represent, respectively, ginseng isolated in leaf and root form or the second in herbal preparation (both preparations derive active compounds similar to ginseng). Molecular docking and in vitro analysis showed that some of the ginsenosides obtained from ginseng root are AChE and BChE inhibitors. Ginsenosides Rb1, Rb2, Rc, Re, Rg1, and Rg3 have a significant inhibitory effect against AChE and BChE. Ginsenoside Re appears to provide the optimal AChE inhibitory activity of a number of ginsenosides.

7.4 Proposals of Western Phytotherapy

Treating diseases with herbs is as old as human civilization, and knowledge about herbs has been around all this time. Native plants and herbs have been used everywhere for centuries against a variety of diseases and have a clear pharmacological activity. In the past, herbal medicines were used as teas and tinctures, poultices, and powders, followed by formulations in mixtures and drinks and, finally, as pure compounds, their extracts. Being handed down from generation to generation, in all cultures, knowledge about the use of medicinal plants exists in the form of local folklore available in families, clans, tribes, and cultures. Medicinal plants or their extracts have been used by humans since the beginning for different diseases, in addition to providing valuable medicines such as cough suppressants (codeine), anti-hypertensives (reserpine), antineoplastics (vinblastine and Taxol) and antimalarials (quinine and artemisinin), analgesics (morphine), and even cardiotonic (digoxin).

The discovery of new herbal medicines continues to provide important clues against several pharmacological targets, including cancer, malaria, cardiovascular disease, and neurological disorders [86]. Plants have proven to be a new source of

natural bioactive molecules. They evolved and adapted over millions of years to resist bacteria, insects, fungi, and climate to produce unique and structurally diverse secondary metabolites. Its ethnopharmacological properties have been used as a primary source of drugs for early drug discovery [29, 71]. According to the World Health Organization (WHO), 80% of people still depend on traditional herbal medicines for primary healthcare [28], and 80% of herbal medicines were related to their original medicines for the ethnopharmacological purpose [27]. Natural products have been used since ancient times in folklore for the treatment of many diseases and illnesses [23]. They have been the source of most of the active ingredients in medicines. This is widely accepted as true when applied to drug discovery in "ancient times" before the advent of the post-genomic era [98]. Despite the recent domain of synthetic chemistry as a method of drug discovery and production, the potential of bioactive plants, or their extracts, to provide new and unprecedented products for the treatment and prevention of diseases is still very expressive [87]. The persistence of chronic illnesses such as diabetes and arthritis, along with the harmful side effects of synthetic drugs, has led to a shift in interest from allopathy to natural/alternative systems of medicine. Compared to chemical synthesis, natural plant-derived products represent an attractive source of biologically active molecules as they are natural and available at affordable prices [37] in addition to having few or no side effects and a sometimes surprising synergy [57]. The conceptual opposition between allopathy and homeopathy is classic in Western medicine. Having consulted the defenders of both currents, in addition to the eloquent and diverse arguments to defend the two consecrated currents, we will find a no less voluminous load of arguments with which each group opposes the presented ideas. A battle a little less exacerbated, but no less voluminous, takes place between phytotherapy and pharmacotherapy from drugs obtained by means of biochemical synthesis or even by biotechnology. To expose the true identity between "botanical people" and "human people," it is necessary to discuss the twin molecular morphology, between the cysteine proteases from our lysosomes and the cysteine proteases from the skin of the green papaya. These enzymes are present and functional in our immune system, in eosinophils, and when parasitic infestations occur, they are released from the cytoplasm of our eosinophils, acting as true biological missiles against invading parasites. Cysteine, a protease from the same papaya species, although green, repels parasitic insects, clogging and digesting their sucking trunks with exactly the same enzyme present in our defense white blood cells. *Homo sapiens sapiens* and *Carica papaya* have been defending themselves against natural attackers with the same molecular weapons for thousands if not millions of years!

What, then, about the many other bioactive molecules present in plants, such as polyphenols, flavonoids, terpenes, resveratrol, caffeic acids, chlorogenic acids, enzymes, etc.?

In the botanical world, these molecules protect the functional parenchyma cells from the sun's ultraviolet radiation, preventing the photo-rupture of delicate and complex organic structures, without which the cascade of biochemical reactions that lead life forward would be impossible. In the human body, they block the

proliferation of ROS, the feared and propagated free radicals, current villains of a large number of causes related to many pathologies. How to face the startling discovery that certainly impressed Dale, when in 1914 he classified the actions of acetylcholine into muscarinic and nicotinic receptors?

This classification was based on the subtypes of cholinergic receptors capable of binding to nicotine and muscarine, respectively, and which respond to cholinergic activation with high affinity. The great protagonists of such a basic discovery: are Amanita muscaria (Lam) and Nicotiana tabacum L. As legitimate plants, our distant relatives in the Kingdom of living beings, could manifest such a great affinity and specificity with our cholinergic receptors?

Our species was placed on the evolutionary scale as the most perfect and complex product. Our central nervous system has a differentiated role in the hierarchy of organs and systems, and, if that wasn't enough, our cholinergic pathway is associated with cognition: the most noble activity among the dominant activities of our nervous system! Therefore, it is questioned how a representative of fungi, originally present in the lowest positions of the botanical scale, far from the more evolved plants, could have such a relevant role, to the point of determining the classification of our muscarinic receptors!

Finally, we will not need to continue demonstrating the affinities, specificities, and potencies of action of substances from the plant world, together with the animal world. We could extend ourselves to the drinking of religious rituals, such as Ayahuasca (*Banisteriopsis caapi*), present in some cultures. In these substances, the action under the scientific eye is similar to a hallucinogen, while in the original cultures, they are forms of connection with the gods, leading to premonitory visions about the fate of some peoples and cultures.

How to place the endocannabinoid system then? Still under study, but already revealing that from essential fatty acids, we produce neurotransmitters that bind to cannabinoid receptors and receptor proteins, expressed throughout our CNS and peripheral areas. And returning to Botany, *Cannabis sativa* itself, still widely used recreationally, but with recognized pharmacological properties, becomes the therapeutic instrument of the agenda, with cannabidiol, one of its components, capable of producing spasmolytic, hypnotic activities and anxiolytics, among others.

We note that, in fact, natural products represent sources of compounds with potential therapeutic implications in AD and other cognitive disorders, as we will demonstrate below. The development of herbal medicines entails the burden of long steps, using extracts with variable levels in research, depending on the time of origin, the time of harvest, and the difficulty of standardization, which are essential in the strict protocols for pharmaceutical development required today. Thus, whenever a plant bioactive substance gives rise to some therapeutic potential, the first step is to try to synthesize it.

All ethnopharmagnostic knowledge accumulated in this first phase of humanity, useful and vital until then, is now presented for a new stage. With the addition of technology, it is presented to control and, in some cases, help to overcome, even, pain and death. Next, we will expose a panel with the most relevant phytochemical inheritances in modern phytotherapy, adopted from the knowledge of ancestral

cultures such as Indian (Ayurvedic) and Chinese, without forgetting other less apparent brutal so important ones.

Traditionally applied herbal preparations were adjuvant therapy to drugs that currently act in the genesis of amyloid, AChE, and cell death. They are extensively tested to offer better therapeutic prospects for improving the learning and memory functions of AD patients. Currently, few herbal medicines are accepted for clinical application. The reasons behind these few approvals seem to be the complex nature of the chemical components in herbal preparations, in addition to the difficulties of standardization. The identification of the active(s) of medicinal herbs can significantly increase the acceptance of medicinal plants in clinical practice. The knowledge about the properties of plant extracts, formulations, and phytoconstituents with preventive and therapeutic effects on AD in animal models contributes to the development of new therapeutic strategies. Issues such as the refractory nature of allopathic treatments used in AD and the high recurrence of side effects may justify the use of herbal medicines as a good alternative. In fact, some human studies have confirmed the beneficial effects of herbal medicines in preventing and treating dementia [26]. Based on the encouraging results of animal studies and the time-proven safety of some of the herbal agents, the use of these agents as adjunctive therapy in conjunction with conventional drugs may be suggested. The therapeutic effects of most of the herbal remedies mentioned here have yet to be unambiguously confirmed in clinical settings [29].

7.4.1 Acetylcholine

All muscarinic receptors (M1 to M5) are located in different parts of the brain. Soon they are directly involved in neurodegenerative disorders like AD and Parkinson's disease. In AD, M1 and M2 receptor agonists are effective in controlling the disease. With the exception of memantine, all drugs approved by the FDA for symptomatic treatment of AD are in the group of acetylcholinesterase inhibitors, but the action decays after the first 2 years of treatment, in addition to the various side effects.

Table 7.5A presents an overview of the source plants of phytochemicals, alkaloids, and flavonoids, involved in the role of stimulants, depressants, and modulators in the cholinergic system.

Below we highlight the most representative plant specimens that act on the acetyl cholinergic system listed in Table 7.5A.

Amanita muscaria

It is a fungus of the *Amanitaceae* family, native to Siberia and North America, known as amanita or fly agaric. It acts as a cholinergic receptor agonist, being more potent than acetylcholine itself, the main asset for such muscarine cholinergic effects. Muscarinic salt has activity similar to acetylcholine, causing, for example, contraction of the equine ureter and carotid artery. It also causes a reduction in

Table 7.5A Vegetal source of compounds which interact with nAChRs and with mAChRs

Vegetal source	Compound	Compound class	Effect	References
Amanita muscaria (L.:Fr.) Lam., a basidiomycete mushroom	(þ)-Muscarine	Alkaloid	Agonist of the M1–M5 mAChRs, producing the same effects as ACh	Daly [19]
Areca catechu L.	Arecoline	Alkaloid	Activation of M2 mAChR, but not of the nAChRs	Houghton and Howes [43]
Atropa belladonna (Solanaceae)	Atropine, hyoscyamine, scopolamine, hyoscine	Alkaloid	Blocking acetylcholine receptors present on smooth muscle, heart muscle, sinoatrial nodes, and atrioventricular of the heart and exocrine glands	Ali-Melkkilä et al. [4]; Katz and Miledi [54]
Compound present in many fruits, vegetables, and medicinal herbs	Luteolin	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100]
Cryptolepis sanguinolenta (Lindl.) Schlt	Cryptolepine	Alkaloid	Antagonist of the M1, M2, and M3 mAChRs	Wink [112]
Delphinium glaucum S. Watson	Methyllycaconitine	Diterpenoid alkaloid	Selective nAChRs a7 antagonist	Yu et al. [117]; Palma et al. [74]
Eremophila debilis (Andrews) Chinnock	30,40,50,5,6,7-hexamethoxyflavone	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100, 101]
Erythrina spp.	Dihydro-b-erythroidine	Alkaloid	Competitive antagonist of a4b2 nAChRs	Houghton and Howes [43]; Kudryavtsev et al. [59]

Table 7.5A (continued)

Vegetal source	Compound	Compound class	Effect	References
Erythroxylon spp.	Ombuin	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100, 101]
Fritillaria imperialis L.	Ebeinone	Alkaloid	Antagonist of the M2 mAChRs	Wink [112]
Galanthus nivalis L.	Galantamine	Alkaloid	Allosteric potentiation ligand that modulates nAChRs to increase ACh release	Kudryavtsev et al. [59]
Galbulimima baccata F. M. Bailey	(þ)-Himbacine	Alkaloid	Antagonist of the M2 and M4 mAChRs	Wink [112]
Genus *Sophora* L., such as *S. alopecuroides* L.	Sophoramine	Alkaloid	Agonist of the nAChRs	Houghton and Howes [43]
Hyoscyamus niger EU.	Hyoscyamine	Alkaloid	Competitive antagonist of acetylcholine	Silva et al. [96]
Laburnum anagyroides Medik.	Cytisine	Alkaloid	Partial agonist of neuronal nAChRs; partial agonist of a4b2 nAChRs	Kudryavtsev et al. [59]; Dey and Mukherjee [20]; Yu et al. [117]
Lobelia inflata L.	Lobeline	Alkaloid	Agonist of the nAChRs	Houghton and Howes [43]
Nicotiana tabacum L.	Nicotine	Alkaloid	Agonist of several subtypes of nAChRs; antagonist of nAChR a9	Kudryavtsev et al. [59]
Pilocarpus spp.	(þ)-Pilocarpine	Alkaloid	Agonist of the M1–M5 mAChRs	Wink [112]

(continued)

Table 7.5A (continued)

Vegetal source	Compound	Compound class	Effect	References
Physostigma venenosum Balf.	Physostigmine	Alkaloid	Increases the concentration of ACh at cholinergic transmission sites. Physostigmine inhibits this action of cholinesterase and thereby prolongs and intensifies the actions of ACh	Triggle and Filler [105]
Scopolia tangutica Maxim.	Atropine and scopolamine	Alkaloids	Very powerful antagonist of the M3 mAChRs	Thal et al. [103]
Tabernanthe iboga Baill.	Ibogaine	Alkaloid	Blocking of the nAChRs (inhibit nAChR-mediated catecholamine release)	Thal et al. [103]
Withania somnifera (L.) Dun.	Sitoindosides VII–X and withaferin A	Sitoindosides (acyl steryl glucosides); withaferin A (steroidal lactone)	Enhancement of M1 mAChR binding sites	Thal et al. [103]

Consultation source, adapted from: Silva et al. [96]

blood pressure. It is an alkaloid, which acts as an agonist at muscarinic receptors M1 to M5 (mAChRs).

Pilocarpus jaborandi Holmes

Known as Indian hemp, it is from the Rutaceae family. It can be found in tropical America and Western India. Its active ingredient is pilocarpine, a potent muscarinic (post-ganglionic) and nicotinic (ganglionic) agonist receptor. It operates from M1 to M5 (mAChRs).

Areca catechu EU

Known as betelnut, areca nut, or Supari (Hindi), it is from the Aceraceae family. Its seeds are used, and the main asset is arecoline, the main phytochemical constituent that stimulates muscarinic receptors in the SNA and CNS. It causes contraction of

the guinea pig ileus and smooth muscle contraction and increases learning and memory, through the type 1 muscarinic receptor, in addition to a vasodilating and antithrombotic effect.

Physostigma venenosum Balf
Known as Calabar and ordeal beans. It belongs to the Fabaceae family, and its main active substance, physostigmine, inhibits acetylcholinesterase in post-ganglionic nerves and myoneural nerve endings (somatic motor neurons). It peripherally and centrally increases the level of acetylcholine depending on the dose. Physostigmine is the most potent cholinesterase inhibitor drug in the treatment of memory loss in an aged primate model. Known commercially for eserine, it is an indirect parasympathomimetic of acetylcholinesterase inhibition. Because it is a tertiary ammonium compound, physostigmine crosses the blood-brain barrier to reverse the central anticholinergic and delirium toxic effects: anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Physostigmine is rapidly metabolized (60–120 minutes) [105].

Atropa belladonna US
Known as belladonna herb, it belongs to the Solanaceae family. Its leaves are rich in atropine, the main active agent, which is a competitive antagonist for muscarinic acetylcholine receptor types M1, M2, M3, M4, and M5. Atropine modifies the acetylcholine/receptor molecular reaction, and conductance is also reduced. Another secondary metabolite is scopolamine, a muscarinic receptor antagonist, also known as an anticholinergic substance. It is enantiomer of hyoscine and l-hyoscine. They are powerfully active as antagonists at muscarinic M3 receptors.

Hyoscyamus niger US
Its active ingredient, hyoscyamine, has two forms, (+) hyoscyamine and (−) hyoscyamine, which is a competitive antagonist of acetylcholine. Widely used as a sedative in pre-anesthesia, it has several other effects that may be involved in the treatment of CNS disorders. Leaves and seeds contain scopolamine (more than 50%), hyoscyamine, and atropine.

Table 7.5B lists the main plant alkaloids, their sources, and their effects on cholinergic muscarinic receptors.

7.4.2 Gamma-Aminobutyric Acid (GABA)

It is a neurotransmitter associated with depressive disorders, indicating that with its excessive decrease, panic and unipolar disorder may arise. Premenstrual syndrome is also related to low levels of GABA. When it is under- or overexpressed, there is likely to be an overexpression of excitatory neurotransmitter. It is always released to balance stimulating firing. Metabotropic Gaba C receptors (marked expression in the retina) have a slow initiation, therefore, longer than the ionotropic GABAA receptor, which conductions more quickly, therefore, with a shorter duration. GABA

Table 7.5B Vegetal products interacting with nAChRs and with mAChRs

Compound	Vegetal source	Compound class	Effect	References
(þ)-Himbacine	*Galbulimima baccata* F. M. Bailey	Alkaloid	Antagonist of the M2 and M4 mAChRs	Wink [112]; Khatoon et al. [55]
(þ)-Muscarine	*Amanita muscaria* (L.:Fr.) Lam., a basidiomycete mushroom	Alkaloid	Agonist of the M1–M5 mAChRs, producing the same effects as ACh	Daly [19]
(þ)-Pilocarpine	*Pilocarpus* spp.	Alkaloid	Agonist of the M1–M5 mAChRs	Wink [112]
30,40,50,5,6,7-hexametoxiflavona	*Eremophila debilis* (Andrews) Chinnock	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100, 101]
Arecoline	*Areca catechu* L.	Alkaloid	Activation of M2 mAChR, but not of the nAChRs	Houghton and Howes [43]
Atropine and scopolamine	*Scopolia tangutica* Maxim.	Alkaloids	Very powerful antagonist of the M3 mAChRs	Thal et al. [103]
Cryptolepine	*Cryptolepis sanguinolenta* (Lindl.) Schlt	Alkaloid	Antagonist of the M1, M2, and M3 mAChRs	Wink [112]
Cytisine	*Laburnum anagyroides* Medik.	Alkaloid	Partial agonist of neuronal nAChRs; partial agonist of a4b2 nAChRs	Kudryavtsev et al. [59]; Dey and Mukherjee [20]; Yu et al. [117]
Dihydro-b-erythroidine	*Erythrina* spp.	Alkaloid	Competitive antagonist of a4b2 nAChRs	Yu et al. [117]; Harvey et al. [42]
Ebeinone	*Fritillaria imperialis* L.	Alkaloid	Antagonist of the M2 mAChRs	Wink [112]
Galantamine	*Galanthus nivalis* L.	Alkaloid	Allosteric potentiation ligand that modulates nAChRs to increase ACh release	Houghton and Howes [43]

Table 7.5B (continued)

Compound	Vegetal source	Compound class	Effect	References
Ibogaine	*Tabernanthe iboga* Baill.	Alkaloid	Blocking of the nAChRs (inhibit nAChR-mediated catecholamine release)	Houghton and Howes [43]
Lobeline	*Lobelia inflata* L.	Alkaloid	Agonist of the nAChRs	Houghton and Howes [43]
Luteolin	Compound present in many fruits, vegetables, and medicinal herbs	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100, 101]
Methyllycaconitine	*Delphinium glaucum* S. Watson	Diterpenoid alkaloid	Selective nAChR a7 antagonist	Yu et al. [117]; Harvey et al. [42]
Nicotine	*Nicotiana tabacum* L.	Alkaloid	Agonist of several subtypes of nAChRs; antagonist of nAChR a9	Kudryavtsev et al. [59]
Ombuin	*Erythroxylon* spp.	Flavonoid	Binding activity to M1 mAChRs	Swaminathan et al. [100, 101]
Pibocine	Far-eEastern ascidian *Eudistoma* sp.	Alkaloid	High potency of binding to nAChR a7	Kudryavtsev et al. [58]
Sitoindosides VII–X, withaferin A	*Withania somnifera* (L.) Dun.	Sitoindosides (acyl steryl glucosides); withaferin A (steroidal lactone)	Enhancement of M1 mAChR binding sites	Houghton and Howes [43]
Sophoramine	Genus *Sophora* L., such as *S. alopecuroides* L.	Alkaloid	Agonist of the nAChRs	Houghton and Howes [43]

Consultation source adapted from: Silva et al. [96]

is about 10 times more potent at the GABA c receptor than at the GABA a receptor. In Table 7.6, the plants and their main compounds that interact with the GABAergic A receptors are listed.

Below we list the most representative specimens of plants and their bioactive molecules that act on the GABAergic system, shown in Table 7.6.

Table 7.6 Vegetable source of compounds which interact with g-aminobutyric acid type A receptors (GABAARs)

Vegetal source	Compound	Compound class	Effect	References
Amanita muscaria (L.:Fr.) Lam.	Muscimol	Alkaloid	Agonist of GABAaRs	Wink [112]
Anamirta cocculus (L.) Wight and Arn	Picrotoxin		More powerful non-competitive antagonist of GABA A receptors	Silva et al. [96]
Camellia sinensis (L.) Kuntz (present in many fruits and vegetables)	Epigallocatechin-3-gallate (EGCG) and apigenin	Flavonoids	Increases synaptic inhibition-mediated $GABA_A$ (EGCG has a stronger effect) Positive secondary modulation of the benzodiazepine drug effect	Silva et al. [96]
Dicentra cucullaria (L.) Bernh.	Bicuculline	Alkaloid	Competitive activation inhibitor of GABA A, also anti-cholinesterase activity	Silva et al. [96]
Eschscholzia californica (Cham.)	(S)-Reticuline	Alkaloid	Positive modulation of a3, a5, and a6 isoforms	Dey and Mukherjee [20]
Ginkgo biloba L.	Bilobalide and picrotoxin	Terpenoids	Receptor antagonists, acting on Cl channels	Fellows and Scofield [29]
Lavandula angustifolia Mill.	Linalool and linalyl acetate	Essential oil	Modulates neurotransmission in GABA A receptors. Anxiolytic	Zali et al. [119]
Magnolia spp.	Magnolol and honokiol	Lignans	Positive allosteric modulation of $GABA_A$Rs, particularly in the a2 subunit; honokiol has a stronger effect than magnolol	Houghton and Howes [43]; Fellows and ScofieldA [29]; Akhondzadeh et al. [2]
Melissa officinalis EU.	Citronellal, rosmarinic acid, cariofilene, geraniol, eugenol	Essential oil	Inhibits GABA transaminase, enhancing GABAergic activity	Akhondzadeh et al. [2]
Valeriana officinalis L.	Valerianic acid	Terpenoid	Direct partial agonist	Fellows and ScofieldA [29]

Consultation source adapted from: Silva et al. [96]

Dicentra cucullaria (L.) Bernh
North American plant known as "Dutch plants." From the Papaveraceae family. Its active ingredient, bicuculline, an alkaloid of phthalide isoquinoline, is a competitive inhibitor of GABA α receptor activation. Its quaternary salts are more suitable for use, due to the greater solubility in water, also having anticholinesterase activity.

Anamirta cocculus (L.) Wight and Arn
Known as Indian berry, fish berry, or raisin nut, it is in the Menispermaceae family. Is originally from the Philippines, East India, Malaysia, and New Guinea. Its main active ingredient picrotoxin is an equimolar mixture of picrotoxinin and picrotin. Picrotoxinin is the most potent non-competitive antagonist of GABA receptor, while picrotin activity is about 50 times less than picrotoxinin. In addition to GABA, picrotoxinin is an antagonist of GABA c receptors, glycine (moderate), and 5-HT3 (weak). Both picrotoxinin and picrotin are equally potent in blocking glycine receptors.

Ginkgo biloba US
Chinese plant known as avenca. It is in the Ginkgoaceae family. Its active substance, a sesquiterpenoid lactone to bilobalide, has a structural similarity to picrotoxinin, being, therefore, an antagonist of GABA a and GABA c receptors. Despite the great chemical similarity to picrotoxinin, while it is a convulsant, bilobalide is an anticonvulsant.

Amanita muscaria
As described above, muscarine, its active ingredient, is a GABA receptor agonist and widely used to study GABA ionotropic receptors. It is a more potent GABA c receptor agonist than GABA a.

Lavandula angustifolia Mill
Known as lavender and khas (Hindi), it belongs to the Lamiaceae family and has traditional use in the therapy of depressive disorder and contains, among other assets, linalool and linalyl acetate. The leaves and part of the flower are mainly used. Lavender oil is used in herbal medicine, providing relaxation in massage therapy. It modulates GABAergic neurotransmission in a GABA receptor, which non-selectively reduces the influx of calcium, increases inhibitory tone, and reduces depression. Lavender herbal extract with imipramine, a synthetic tricyclic antidepressant, has a synergistic effect and is more effective in depression.

Melissa officinalis EU
Herbaceous plant of the Lamiaceae family, which contains citronellal, linalyl acetate, caryophyllene, geraniol, rosmarinic acid, and eugenol. The essential oils are used in aromatherapy; it contains eugenol that calms the muscles. The lemon balm extract contains rosmarinic acid that inhibits GABA transaminase by increasing GABAergic activity in the brain providing a calming effect on depression and also on anxiety. Neurotransmitters are chemical messengers in the human body and are associated with several CNS disorders. Vegetable drugs can be used as neurotransmitter agonists/antagonists/modulators to treat CNS disorders such as Alzheimer's disease, Parkinson's disease, etc.

7.4.3 Glutamate

It is an excitatory neurotransmitter, and its overexpression can lead to Parkinson's disease. In the Table 7.7 are listed the main compounds from vegetable sources which interact with glutamate receptors.

Below are some of the most prominent plant sources of glutamate receptors, listed in Table 7.7.

Panax ginseng

Based on results, pre- and post-treatment with ginseng have protective effects against Alzheimer's disease induced forgetfulness and memory impairment. The effects of ginseng can be mediated by an increase in the levels of BDNF (brain-derived neurotrophic factor) and antioxidants in the brain's hippocampus region. It decreases the ionic current mediated by NMDARs by antagonists that selectively inhibit NMDAR through polyamine binding (ginsenoside 20(s)-Rh2) or glycine binding (ginsenoside 20(S)-Rg3) sites.

Table 7.7 Vegetal source of compounds which interact with ionotropic and metabotropic glutamate receptors

Vegetal source	Compound	Compound class	Effect	References
Acacia willardiana Rose	Willardine	Alkaloid	Agonist of AMPARs; has been used as a scaffold to produce antagonists, in order to inhibit excitotoxicity associated with AMPAR and kainate activation (GluK1 subunits)	More et al. [72]; Foust and Kaspar [30]
Acacia willardiana Rose	Willardine	Alkaloid	Selective agonist of the KARs that contain the GluK1 subunits	Jane et al. [46]
Achyranthes bidentata Blume	Polypeptides	Polypeptides	Diminution of NMDA-induced intracellular $Ca^{2þ}$, through modulation of the NR2A and NR2B receptor subunits	Cahlíková et al. [13]; Liang et al. [66]
Acorus gramineus Sol. Aiton.	a- and b-asarone and eugenol	Phenylpropanoids	Neuroprotection against excitotoxicity induced by NMDA or glutamate; increase cell survival; inhibition of $Ca^{2þ}$ influx	Liang et al. [66]
Camellia sinensis				Saeed et al. [91]; Levites et al. [65]

Table 7.7 (continued)

Vegetal source	Compound	Compound class	Effect	References
Citrus aurantium L.	Nobiletin	Flavonoid	Reverses the NMDAR antagonism by activation of ERK signaling Increases protein kinase A (PKA) activity and phosphorylation of GluA1 (AMPAR), increasing the post-synaptic response to glutamate	Nakajima et al. (2007) [123]
Coffee flowering plants	Caffeine	Xanthine	Acts in post-synaptic sites, blocking the increase of intracellular Ca2+ as a result of the activation of mGluRs	Yoshimura (2005) [124]
Curcuma longa L.	Curcumin	Curcuminoid (diarylheptanoid)	Inhibitory effects against NMDA stimulation, by decreasing NR1 subunit phosphorylation; decreases the expression of mGluR5, inhibiting glutamate release and consequent excitotoxicity	Liang Wet al. [66]; Mateucci A et al. [125]
Fungi *Eupenicillium shearii* Stolk & Scott	Kaitocephalin	Alkaloid	A competitive antagonist of AMPARs, which acts on GluA2 and inhibits the mechanisms of excitotoxicity; it has higher affinity for NMDARs than for AMPARs	Ahmed et al. (2012) [126]
Gastrodia elata Blume	Gastrodin	Phenolic glycoside	Suppression of glutamate release induced by NMDAR activation	Liang Wet al. [66]
Glycyrrhiza glabra L.	Isoliquiritigenin	Flavonoid	Binds to the NMDAR, inhibiting the increase of the $Ca^{2þ}$ influx into cells induced by glutamate	Cahlíková et al. [13]

(continued)

Table 7.7 (continued)

Vegetal source	Compound	Compound class	Effect	References
Grapes, peanuts, blueberries, and dark chocolate	Trans-resveratrol	Stilbene	Increases the levels of AMPAR proteins through increasing intracellular $Ca^{2þ}$ levels and the consequent activation of AMPK (AMP-activated kinase) and through PI3K/Akt signaling pathway Inhibition of excitotoxicity associated with post-synaptic KARs	Wang et al. (2015) [135]
Huperzia serrata (Thunb.) Trevis.	Huperzine A	Alkaloid	Block of toxicity induced by NMDAR, possibly by binding to the channel pore	Liang Wet al. [66]
Platycladus orientalis (L.) Franco	Methoxypinusolidic acid	Diterpene	Binds to the NMDAR; inhibition of excitotoxicity induced by glutamate, stabilizing $Ca^{2þ}$ homeostasis and attenuating oxidative stress	Cahlíková et al. [13]
Scrophularia ningpoensis Hemsl.	8-O-E-p-Methoxycinnamoyl--harpagide (55) and harpagide	Iridoids	8-O-E-p-Methoxycinnamoyl--harpagide suppressed NMDA-induced cell death more specifically than harpagide; harpagide suppressed NMDA- and kainate-induced cell death	Liang Wet al. [66]
Tabernanthe iboga Baill.	Ibogaine	Alkaloid	Blocking of the NMDARs	Houghton and Howes [43]
Uncaria rhynchophylla Miq.	Rhynchophylline and isorhynchophylline	Alkaloids	Inhibition of NMDA-induced current	Liang Wet al. [66]
Valeriana officinalis L.	Isoborneol	Monoterpene	Inhibitory effect on NMDARs when present at low concentrations	Valle-Mojica et al. [107]

Table 7.7 (continued)

Vegetal source	Compound	Compound class	Effect	References
Panax ginseng C. A. Mey	Ginsenosides protopanaxatriol (ginsenosides 20(S) eRh$_2$ and ginsenosides 20(S)-Rg$_3$)	Triterpene saponins	Decrease ionic current mediated by NMDARs; antagonists that selectively inhibit NMDAR through the polyamine binding (ginsenoside 20(s)-Rh$_2$) or glycine binding (ginsenoside 20(S)-Rg$_3$) sites	Cahlíková et al. [13]; Khatoon et al. [55]; Silva et al. [96]

Consultation source adapted from: Silva et al. [96]

Tabernanthe iboga Baill

From the Apocynaceae family known as iboga, it contains an indole alkaloid, ibogaine, which is a non-competitive antagonist of NMDA receptors.

Camellia sinensis (L.) Kuntz

It is commonly known as green tea and is native to China and India. It belongs to the family Theaceae. The main chemical constituent theanine is an NMDA receptor antagonist. Theanine prevents the death of rat cortical neurons in culture induced by glutamic acid. Although the binding capacity in all cases is markedly less than that of glutamic acid, theanine has a greater affinity for AMPA/kainite receptors than for NMDA receptors. One study reported that green tea extracts defended dopaminergic neurons against damage caused by reactive oxygen species, NO, NO inducible synthase, lipid peroxidation, nitrite/nitrate content, and protein-linked 3-nitrotyrosine due to the exposure of mice to 6-hydroxydopamine [91]. Thus, green tea extract has protective roles in Parkinson's disease. Theanine crosses the blood-brain barrier; it has been shown in rats that theanine, upon reaching the brain, increases the production of serotonin and dopamine. L-Theanine has recently been linked to increased learning ability in animals and the induction of relaxation in humans, possibly due to its effect on serotonin, dopamine, and other neurotransmitters.

Also present in *Camellia sinensis*, epigallocatechin-3-gallate (EGCG), due to its antioxidant property, prevents neurotoxicity caused by β-amyloid in neuronal cells of the hippocampus. The processing of APP through the activation of PKC, for soluble non-amyloid gene APP (sAPP), thus avoiding the formation of neurotoxic β-amyloid [65, 91]. EGCG and other catechins found in green tea inhibit the enzyme aβ secretase (BACE1), which is involved in the conversion of sAPP to β-amyloid, so the production of β-amyloid is inhibited [210, 211]. Several studies have reported that green tea components like EGCG prevent injuries caused by Parkinson's disease [91].

7.4.4 *Phytocompounds Absorbed by Western Pharm Therapy*

As studies and tests using phytochemicals evolve, and starting from the bench, for "in vitro" models and then for animal models to finally test in clinical trials, some already in phases II and III, the health authorities begin to recognize their effectiveness as demonstrated below. Although this movement has been slow and steady, with the adoption of isolated and /or associated compounds in therapies with natural compounds purely, as well as in mixed clinical applications, associating allopathic chemotherapy aided by phytotherapy, which exhibit promising results.

Table 7.8 summarizes the main plant-based compounds approved by the FDA (Food and Drug Administration).

Table 7.8 FDA-approved plant-derived compounds against AD

Phytocompound	Product name	Plant source	FDA-approved	Clinical trials	Targets	References
Curcumin	Longvida	*Curcuma longa* (Zingiberaceae)	_	Phase III	Anti-amyloidogenic, anti-inflammatory, anti-ChE, anti-β-secretase	Kumar et al. [61]
Galantamine	Razadyne	*Lycoris radiata* (Amaryllidaceae)	2001	_	Reversible inhibition of AChE and allosteric potentiation of nicotinic ACh receptors	Kumar et al. [61]
Huperzine A	_	*Huperzia serrata* (Lycopodiaceae)	_	Phase III	Restores cognitive deficits by reversibly inhibiting AChE	Kumar et al. [61]
Resveratrol	_	*Vitis vinifera* (Vitaceae)	_	Phase III	Prevents cognitive impairments and associated oxidative stress by reducing plaque formation	Kumar et al. [61]
Rivastigmine	Exelon	Physostigma	2000	_	Inhibits AChE in the cortex and hippocampal region	Kumar et al. [61]

Consultation source adapted from: Silva et al. [96]

The main families of compounds effective in AD therapy are listed in Table 7.9 below, where it shows their pharmacological targets.

In Table 7.10, on the following pages, there is a summary of the proposed mechanisms of the most common phytochemicals in AD.

Table 7.9 Plant-derived alkaloids effective in AD

Class of alkaloids	Alkaloids	Plant source	Targets	References
Capsaicinoid	Capsaicin	Hot chili peppers of plant genus *Capsicum*	Ameliorates synaptic damage and tau hyperphosphorylation	Sharma et al, (2019) [95]
Indirubin	Indirubin-3′-monoxime	Indigo naturalis	Kinase inhibitor, GSK-3β inhibitor, prevents abnormal tau phosphorylation	Ding et al. (2010) [129]
Indole alkaloids	Geis spermine	*Geissospermum vellosii*	Inhibits AChE	Choudhury et al. (2014) [130]
Indole β-carboline	Harmine	*Peganum harmala*	Inhibits AChE and DYRK1A catalyzed phosphorylation of tau	Choudhury et al. (2014) [130]
Isoquinoline alkaloids	Berberine	*Hydrastis canadensis*, *Coptis chinensis*, *Berberis aquifolium*, *Berberis vulgaris*, *Berberis aristata*	Attenuates Aβ, reduces BACE-1 activity, prevents hippocampal neurodegeneration, inhibits MAO and AChE	Imenshahidi et al. (2014); Jiang et al. [131] (2015) [132]
	Morphine	*Papaver somniferum*	Binding to μ-opioid receptor (MOR) in CNS which increases the levels of γ- aminobutyric acid in synapse of the brain, protects against intracellular Aβ (iAβ) venomousness, reverses the iAβ-induced electrophysiological changes	Cushnie et al. (2014) [133]
	Salsoline	*Salsola opositifolia*	Inhibits AChE enzyme	Zhu et al. (2014) [134]
	Galantamine	*Narcissus tazetta*, *Galanthus nivalis*, *Leucojum aestivum*	Neuroprotective role, inhibits AChE enzyme, Aβ accumulation and cytotoxicity, ROS scavenging activity	Sharma et al, (2019) [95]

(continued)

Table 7.9 (continued)

Class of alkaloids	Alkaloids	Plant source	Targets	References
Lycopodium alkaloid	Huperzine A	*Huperzia serrata*	Neuroprotective role, mitochondrial protection from Aβ aggregation-induced toxicity, inhibitor of Aβ, also promotes reduction of BDNF	Xing et al. [136]
Piperidine alkaloids	Piperine	*Piper nigrum* and *Piper longum*	Neuroprotective, inhibits AChE and β-secretase enzymes, attenuates oxidative stress and cognitive deficits	Hritcu et al. [137]
Pyridine alkaloids	Nicotine	*Nicotiana tabacum*	Prevents the Aβ peptide accumulation and neuroprotective action	Choudhury et al. [130]
Pyrroloindole alkaloids	Physostigmine	*Physostigma venenosum*	Inhibits AChE	Kumar et al. [138]
Tetracyclic oxindole alkaloids	Rhynchophylline and isorhynchophylline	*Uncaria rhynchophylla*	Neuroprotective, antioxidant, inhibit tau protein hyperphosphorylation, reverse the Aβ phosphorylation of Akt, cAMP response element-binding protein, and GSK-3β signaling proteins	Xian et al. [127, 139]

Adapted from: Sharma et al. [95]

Table 7.10 Synopsis of mechanisms of important medicinal plants against AD

Mechanism	Phytochemical	Plant extracts
Anti-amyloid aggregation effect		*Ginkgo biloba*, *Crocus sativus*, *Curcuma longa*, *Uncaria rhynchophyliia*
Anti-apoptotic		*Bacopa monniera*, *Curcuma longa*, *Centella asiatica*
Antioxidant activity		*Desmodium gangeticum*, *Ginkgo biloba*, *Moringa oleífera*, *Salvia officinalis*
Cholinesterase inhibition		*Achyrocline tomentosa*, *Eupatorium viscidum*, *Ruprechtia apetala*, *Trichocline reptans*, *Zanthoxylum coco*, *Poncirus trifoliata*, *Treculia obovoidea*, *Angelica archangelica*, *Cassia obtisufolia*, *Desmodium gangeticum*, *Salvia officinalis*
Modification of monoamines		*Moringa oleífera*
Neuroprotective		*Bacopa monniera*, *Benincasa hispida*, *Celastrus paniculatus*, *Glycyrrhiza glabra*

Table 7.10 (continued)

Mechanism	Phytochemical	Plant extracts
Phosphodiesterase inhibitors	Flavonoids	*Euchresta japonica*, *Scutellaria* spp., *Sophora* spp., *Butea monosperma*
	Alkaloids	*Picrasma quassioides*, *Ailanthus altissima*, *Nelumbo nucifera*
	Saponins	*Lilium regale*, *Lilium henryi*, *Periandra dulcis*, *Allium chinense*
	Lignans	*Cassia obtisufolia*, *Glycyrrhiza glabra*, *Caesalpinia sappan*
	Coumarins	*Glycyrrhiza ularensis*, *Crindium monnier*, *Angelica pubescens*
	Essential oils	*Haplopappus rigidus*, *Satureja parviflora*, *Senecio eriophyton*
Prevents neuroinflammation		*Centella asiatica*, *Tinospora cordifolia*, *Curcuma longa*, *Emblica officinalis*, *Withania somnifera*

Consultation source adapted from: Sharma et al. [95]

To conclude the panel of phytochemicals, we could not leave out adaptogenic phytotherapies, a relatively new concept, originating from Russian Science, in the 1950s, and which researched "super herbs" capable of providing superior resistance to stress in general.

7.4.5 Adaptogenic Phytotherapies and New Ways

The most convincing clinical evidence for the effectiveness of adaptogens has been observed in studies related to their neuroprotective effects and effects on cognitive functions in case of fatigue, as well as their effectiveness in states of asthenia and depression [33]. Adaptogenic herbs, sometimes called "super herbs," were listed among the main health and wellness trends of 2016 by many of the mainstream media. The term "adaptogen" first appeared in the scientific literature in the late 1950s, when it was loosely defined as any substance that promotes "nonspecific resistance" to stress. In general, adaptogens are nontoxic substances that promote the normalization of bodily functions and support a healthy response and resistance to "harmful factors" or stressors.

Hypericum perforatum
This plant contains as bioactive phytochemicals hypericin, hyperforin, and pseudohypericin belonging to the phytochemical family of naphthodianthrones, which acts on serotonin receptors.

Myrciária jaboticaba
The hyperphosphorylation of the tau (tau) protein that occurs in the microtubules in the hippocampus can be caused by resistance to central and peripheral insulin, and these changes are related to the development of tauopathies, such as Alzheimer's

disease. The bark of *Myrciária jaboticaba* has phenolic compounds (e.g., cyanidin, ellagic acid), dietary fiber, and carotenoids, which contribute to a great antioxidant capacity. To elucidate the phytotherapeutic properties, a trial with forty adults Swiss mice as animal model is presented, supplemented with a high-fat diet with 4% *Myrciária jaboticaba*, were divided into four groups of 10 and fed and supplemented for 10 weeks. The group treated with jaboticaba showed less phosphorylation of tau in the hippocampus, corroborating a better learning/memory performance in the Morris water maze test. The maintenance of neuronal viability, lower levels of hippocampal inflammatory markers, and better brain antioxidant defenses were also related to the consumption of *M. jaboticaba* bark. These findings contribute to a better understanding of how a high-fat diet supplemented with jaboticaba peel neutralizes the impairment of cognitive functions caused by eating a high-fat diet and insulin resistance induced by the diet [24].

And more recently, along with nootropic substances, which are metabolically targeted to the brain, the concept of neuropaths, endogenous substances, capable of stimulating neurogenesis, that is, the replacement of dead neurons, appears. Some substances of plant origin can stimulate and accelerate this process in comparison with the physiological process, without supplementation.

Cyanidin-3-O-glucoside, ellagic acid, and carotenes, the main antioxidant compounds in the bark of jaboticaba, are able to pass through the blood-brain barrier to be available in the brain parenchyma [16, 99, 114]. There they play a direct role in the modulation of neuronal receptors, kinases, transcription factors, neurotrophins, synaptic plasticity, and other enzymes or proteins linked to the antioxidant system and inflammatory and insulin cascades, in addition to acting as reactive oxygen scavengers [47, 88, 89].

7.4.5.1 Neurotrophins: A New Way

Neurotrophins (neurotrophic factors) have been shown to be potentially beneficial in the treatment of neurodegenerative diseases, such as Parkinson's disease (PD) and Huntington's disease (HD), because endogenous neurotrophic factors have been recognized for playing critical roles in promoting neurogenesis, differentiation, and neuroprotection throughout the development of the central nervous system [45, 108]. In mammals, the known neurotrophins are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4) [45]. These neurotrophins bind selectively to their tyrosine kinase receptors TrkA, TrkB, and TrkC, and they all bind non-selectively to the neurotrophin p75 receptor, resulting in the activation of neuronal signal transduction related to the broad spectrum of biological activities exerted by neurotrophins [33, 108].

Marapuama (Ptychopetalum olacoides)

In popular medicine in Brazil, marapuama (Ptychopetalum olacoides) is used as a tonic in the treatment of degenerative diseases of the nervous system; from the MeOH extract of this plant, a series of clerodane diterpenes have been isolated, among which

pticonal hemiacetal, 6α,7α-dihydroxyanonene, and 7α,20-dihydroxyanonene exhibit NGF (nerve growth factor) enhancing activity in PC12 cells [33].

Pink Rhodiola (Santolina chamaecyparissus DC. Dyman)
The extracts affected many genes playing key roles in modulation of adaptive homeostasis, indicating their ability to modify gene expression to prevent stress-induced and aging-related disorders. Overall, this study provides a comprehensive look at the molecular mechanisms by which adaptogens exert stress-protective effects [75].

7.5 The Alliance of Phytotherapy with Nanotechnology

The blood-brain barrier (BBB) limits the transport of many therapeutically important drugs from the blood to the brain, including anticancer drugs, antibiotics, and a wide variety of drugs active in the central nervous system (CNS), especially macromolecules, such as neuropeptides and proteins. It is formed by the endothelial cells of the brain capillaries that essentially constitute the main exchange interface between the blood and the brain. The limiting function also occurs in the arachnoid membrane and in the ependymal cells that surround the circumventricular organs of the brain. The blood-brain barrier (BBB) is a vital element in regulating the constancy of the brain's internal environment, in addition to protecting the CNS from harmful circulating substances and maintaining essential brain homeostasis, but as a result, it constitutes an important obstacle and impediment to the effective treatment of many brain diseases. A number of different strategies have been devised to overcome this barrier, recently, such as the osmotic opening of the narrow junctions and the direct surgical administration of drugs in the brain [38]. The most notable progress, however, has been achieved through the use of nanotechnology. Most of the drugs on the market are not effective in the treatment of this type of disease, as they are not able to permeate the blood-brain barrier (BBB). Lipid nanoparticles are nano-systems that allow us to overcome this problem, since they have the capacity to overcome this biological barrier and reach its therapeutic target. This specific type of nanoparticles has several advantages over other types of nanoparticles, such as greater stability, greater load capacity, less cytotoxicity, allowing controlled release of the drug, and having a relatively low production cost [39]. Several studies show the variables that influence the transport of drugs to the CNS and the mechanisms that have been developed to make this transport more effective. For example, liposomes, as well as nano-solid lipid carriers or different polymeric nanoparticles [10, 12], have been used successfully to transport drugs through the BBB to the brain. These drugs included neuroactive peptides [12, 34] as well as the cytostatic drug doxorubicin.

Doxorubicin after binding to polysorbate 80-coated nanoparticles significantly reduced the growth of glioblastoma 101/8 malignant brain tumor, transplanted intracranially, very aggressive, and led to the disappearance of the tumor in about 20–40% of the animals after intravenous injection [11, 121]. In addition to increased transport of nanoparticles to the brain, these nanocarriers also protect the active agent from enzymatic degradation, appear to circumvent the ABC effect of flow

transporters, and, in addition, are able to reduce side effects [1, 128]. The mechanism by which nanoparticle delivery systems achieve drug transport through the BBB, however, has so far not been fully explained and has attracted considerable debate. It has been suggested that nanoparticle systems exert a widespread toxic effect on the BBB permeabilization narrow junctions and allow cellular movement of solutes to the brain [93]. Subsequent studies have not shown toxic effects, in vivo and "in vitro," in the doses normally used. They also showed that, in order to be delivered to the CNS, a drug must be attached to the nanoparticle before intravenous administration, which would not be a requirement if opening of the watertight junction was involved. These later studies clearly show that subsequent studies have not shown toxic effects, in vivo and "in vitro," in the doses normally used. They also showed that, in order to be delivered to the CNS, a drug must be attached to the nanoparticle before intravenous administration, which would not be a requirement if opening of the watertight junction was involved. Is very difficult to bypass the blood brain barrier and these remarkable properties should be demonstrated, because the normal and regular drugs cannot do it. There are several mechanisms, transporting lipoproteins through the BBB. The strategy of modifying this nanoparticle with Apolipoprotein E will make it interact with these receptors of apolipoprotein in the blood-brain barrier and results in its endocytosis uptake to the endothelium and possibly transcytosis to the brain. This suggestion is supported by the observation that nanoparticles with apolipoprotein E (ApoE) adsorbed or covalently linked transport drugs linked equally well through the BBB [93].

The success in transporting drugs to the CNS is an arduous challenge, due to the presence of anatomical and physiological barriers, which regulate the passage of endogenous and exogenous molecules to the cerebral parenchyma. It is challenging to achieve a therapeutic effect of drugs with action at the CNS level and that needs to overcome these barriers in therapeutic concentrations. The blood-brain barrier is a complex and dynamic structure that separates blood from the brain and that has a fundamental role in maintaining CNS homeostasis. During the last three decades, several efforts have been made to solve this problem, and several strategies have been proposed. More recently, nanoscience and nanotechnology have made it possible to consider nanotransporters as a possible solution. The nanoparticles, if modified, can present a certain tropism to the luminal surface of the BBB and reach the brain parenchyma through transcytosis. Despite being a promising strategy, only a few drugs incorporated in nanotransporters are still available on the market [34, 35].

7.5.1 Lipid Nanoparticles (NLs)

They were developed in the early 1990s and have been shown to be able to overcome these problems. Thanks to their lipidic nature, they are biodegradable, which makes them less toxic than other types of nanoparticles. In addition to this characteristic, they have a reduced size, which prolongs their circulation time in the bloodstream, their large-scale production is feasible, and they are able to prevent the "one-shot"

release, which could generate an increase in release toxicity of a large amount of drug. BBB selects and prevents the entry of toxic agents, largely due to the endothelial cells located on the walls of blood vessels. Such endothelial cells have particularities that are essential for their selective barrier function in the CNS. They have two types of junctions between adjacent cells, known as adhesion junctions and occlusion junctions. Adhesion junctions participate in the adhesion of endothelial cells to each other, in the initiation of cellular polarization, and in the regulation of cellular permeability. The occlusion junctions separate the apical and basolateral domains, causing cellular polarization and restricting the passage of ions, hydrophilic compounds, and macromolecules through paracellular transport. These junctions also create a high transendothelial electrical resistance (TEER) between the blood and the brain, which generates a limited passive diffusion of compounds through the BBB. But there are other mechanisms that contribute to this barrier function of BBB. The light surface of endothelial cells expresses P-glycoprotein (GpP), an ATP-dependent transporter protein, belonging to the ABC transporter family. Through an efflux system, GpP prevents hydrophobic substances from crossing the BBB. The problem lies in the fact that several drugs that are candidates for reaching the CNS are substrates for ABC transporters, so their therapeutic range will be limited. The enzyme barrier also plays a fundamental role in protecting the CNS. A wide range of enzymes, such as acetylcholinesterase, alkaline phosphatase, gamma-glutamyl transpeptidase, and monoamine oxidase, are able to degrade different chemical compounds that can overtake BBB and reach the brain. In addition to endothelial cells, BBB is composed of a diversity of cells, such as pericytes, astrocytes, neurons, and microglia, which give them biochemical properties and their specialized structure.

The pericytes are separated from the endothelial cells by the basal lamina. These cells are associated with neovascularization, angiogenesis, and blood vessel stability. Astrocytes interact with endothelial cells in order to ensure adequate neuronal function and control of cerebral blood circulation. They control potassium levels, inactivate neurotransmitters, and regulate and produce growth factors and cytokines. They are undoubtedly essential cells for CNS homeostasis.

The microglia function as immunocompetent cells in the brain. In turn, neurons affect endothelial cells by promoting the synthesis and release of occludine to the periphery of cells. Occludin is part of the composition of the occlusion junctions present between endothelial cells, and the role of neurons will thus be important in the stability of the junctions and, consequently, the BBB. In addition to protecting the CNS, BBB has other functions of equal importance such as:

(i) Selective transport of molecules that provides essential nutrients for the proper functioning of the nervous system.
(ii) Eliminate waste products.
(iii) Regulate homeostasis in the brain.

Small molecules and gases in the blood, such as oxygen and carbon dioxide, passively diffuse through the BBB, while essential nutrients such as glucose and amino acids need specific transport proteins to reach the brain.

7.5.2 Transcytosis

Transcytosis is a cellular absorption process aimed at the transport of macromolecules, and its purpose is the recycling or translocation of components of the plasma membrane. Transcytosis is more common in epithelial cells, and can occur in other cells, such as blood capillaries, specifically active transcytosis, which is also observed in neurons, osteoclasts, and intestinal M cells. A vesicle is formed containing the endocytic element, which moves through the cytoplasm and merges with the cytoplasmic membrane, thus promoting its release into the extracellular matrix (the vesicle membrane canals transport macromolecules). The process involves transferring elements through cells to opposite cell domains (usually occurring in polarized cells) and is common, for example, in epithelial and endothelial cells, but it is also an important mechanism for distributing membrane proteins in some cells. Transcytosis depends on the cytoskeleton, actin microfilaments (have a motor role), and microtubules (indicate the direction the vesicles must follow). This type of transport is extremely important for substrates to be able to enter the apical part (part facing the lumen) of the cell and, through it, exit through the basal part (side facing the basal membrane). When the substrates bind to specific receptors present in the apical region of the cell, the vesicle-forming proteins, clathrin and caveolins – proteins that encapsulate the material and fuse it to an initial endosome, starting the process. However, before going to the other side of the membrane, these vesicles pass through the recycling endosome. Then the passage of the substrate through the recycling endosomes is important because it is there that the cells are able to carry out regulation. Then the regulation of transcytosis is a complex process that can vary a lot (depending on the tissue in which it is occurring), and with this, several specific mechanisms of tissue transition have been identified [34, 35].

Examples of transported macromolecules are IgA, transferrin, and insulin.

Nanoparticles of human serum albumin coated with covalently bound ApoE are clearly absorbed in brain endothelial cells by endocytosis after injection into the bloodstream. A certain proportion of these particles are also transported to the brain parenchyma. This movement to the internal compartments of the CNS can only be carried out by transcytosis throughout the BBB. Although it is not observed, a reuptake of particles by neurons must occur. An opening or modulation of the closed junctions of the cerebral endothelium does not appear to occur, and nanoparticles have never been observed in association with tight junction complexes or within the cell space. Polysorbate-coated nanoparticles also appear to deliver drugs to the CNS by a similar mechanism after the adsorption of ApoE into the circulation after intravenous injection.

So, there are some experiments carried out, proving in an animal model that the administration of nanoparticles in the bloodstream, with functionalization of the envelope membrane surface through apolipoprotein E, covalently linked, allows diffusion in all murine nervous tissue after about 30 minutes as demonstrated [120].

Bioactive molecules from plant extracts could be encapsulated by nanoparticles like *nano-solid lipid carriers*, according to the technique specifically developed for Bio-Omega, a product composed of fish oil nanoparticles, rich in EPA and DHA, enclosed in a mix of vegetable phytosterols, such as fatty acids like stigmasterol, campesterol, brassicasterol, and sitosterol, among others. Such an arrangement constitutes a product, which is composed of solid lipid nanocarriers, with a nuclear portion of fish oil and a wrapping portion of vegetable cholesterol. In order to structure the new proposal, to supplement DA patients with nano-therapy supplements, as previously mentioned, one must overcome the challenge of passing through the liver. The tactic is to make the first pass through the liver with particles of suitable size, between 100 and 200 nm, very similar to the size of the human chylomicron, and with a chemical composition on the surface of the particle similar to human cholesterol, plant phytosterols. Such a maneuver indicates that these particles pass through the hepatic sinusoid without "screwing," passing freely, without biochemical disassembly, allowing its entry into the systemic current, without modifications, carrying the bioactive molecules important for the treatment of AD, and diffusing in the central nervous system, via vessels, with simultaneous transcytosis and cellular penetration into the cerebral parenchyma. Below we can see some illustrative images in the (Fig. 7.1) with the nanoparticles in the form of nano-solid lipid carriers which were produced with eicosapentaenoic and docosahexaenoic acid inside

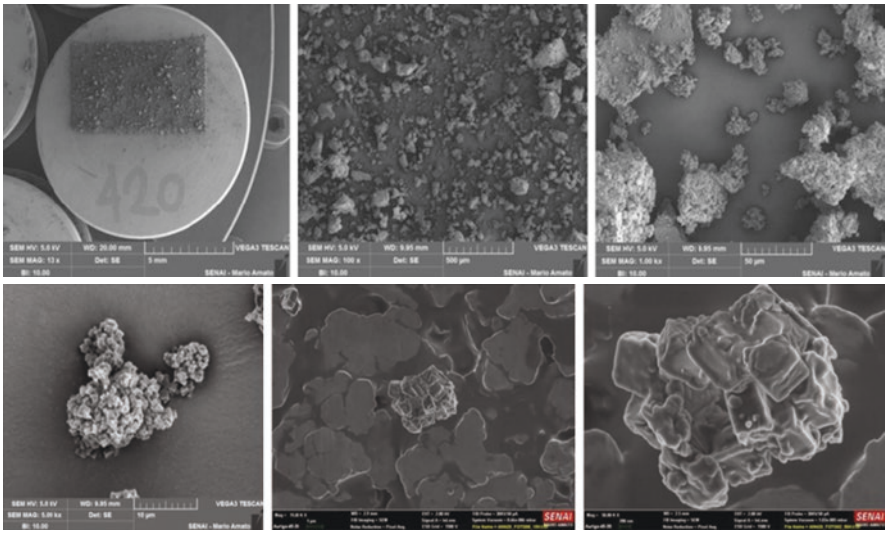

Fig. 7.1 Author's collection: "Nanoparticles capable of performing Transcytosis" Images by scanning electron microscopy of NLC (structured nano-lipid carriers), several increasing magnifications from 13 X to 50,000 X of fish oil particles (eicosapentaenoic acid and docosahexaenoic acid) nanostructured, with vegetable fats in its coating (campesterol, stigmasterol, brassicasterol, among others), FAPESP project Bio-Omega/2018. Note, in the increase of 50,000 X, the last at right below, the conformation of the phytosterol crystals encompassing the liquid oil core

and which can be administered in the form of nutraceutical supplements such as shakes, nutritious bars, and yogurts, among other presentations, in order to facilitate the adherence to treatment, that is, problematic in AD. Next, there may be doubts about the repertoire of bioactive molecules reviewed throughout the chapter and their inclusion in solid lipid nanocarriers. Some candidates such as curcuminoids are already being nanoencapsulated, and soon we will include them in nutraceutical drinks for the senile population. This experimental phase can and should be reported in compendiums like this, so that the health team, focused on cases of AD, can wait and charge the product and its pertinent clinical trials. Industry researchers nourish themselves with knowledge from Basic Science but are committed to turning them into safe and effective technology, in the shortest possible time!

We can say that without a doubt the fat-soluble molecules will be well encapsulated by this technique, but what about the water-soluble ones? And those that are insoluble or that have low solubility and consequently low bioavailability? What to say about the thermal limitations so common to polyphenols, terpenes, and other antioxidant molecules. The choline itself, a vital amino acid for the production of acetylcholine?

Let us start by explaining that other techniques can safely meet the new demands placed.

For the water-soluble bioactive molecules and part of the insoluble ones, it is possible to propose the modified ionotropic gelation that we have just developed on the bench and will soon become an industrial pilot. In this project, we encapsulate curcuminoids extracted using the supercritical extraction technique, using CO^2 scavenging, with repeated indications in previous passages, Indian medicine and Western phytotherapy. It consists of modified ionotropic gelation, with sodium alginate as a gelling phase and calcium chloride, responsible for the exchange of ions, with modification in the way of obtaining the particles, in order to achieve the smallest diameter of the curcuminoid nucleus, possibly sub-micron.

In order to allow the posterior coating, after gelation, with functionalizing fatty acids, by coating in chilling spray, the gelled nanocapsules are left for 24 hours in a thixotropic curing and stiffening process, before chilling.

The end result is a powder, easily dispersible in a milk shake, or not, flavored in order to increase palatability, such as chocolate, vanilla, strawberry, or banana. The flavor and texture, as well as the variety of flavors, are important, given the need for daily dose repetition, over the years of AD survival.

7.5.3 Transport Mechanisms Through BBB

The vast majority, more than 90% of new molecules potentially effective for the treatment of CNS diseases, are not able to cross the BBB. Low molecular weight lipophilic molecules, with 500 Da or less, are able to permeate the BBB and reach a concentration in the CNS that is pharmacologically effective [34]. There are many mechanisms for permeation of soluble molecules through the BBB, for example,

the transcytosis and diffusion to cell that occurs between endothelial cells, being non-saturable and non-competitive processes. Only small water-soluble molecules are able to cross the BBB through this mechanism, since the occlusion junctions limit this type of transport [34, 35].

7.5.4 Pharmacological Carriers for the Central Nervous System: Lipid Nanoparticles

Transcellular diffusion occurs through endothelial cells, intracranial vessels, being a non-competitive and also not a saturable mechanism. To use this transport mechanism, the molecules must be lipophilic. The essential nutrients reach the CNS because then transport proteins are used, which are found on the surface of endothelial cells. These proteins recognize their specific substrate, allowing selective transport of molecules to the CNS. There are specific carrier proteins for the transport of certain nutrients such as glucose, amino acids, nucleosides, galactose, vitamins, and hormones, which adapt to the metabolic needs of the brain and the concentration of substrates in the plasma. Another mechanism for transposing BBB is transcytosis mediated by receptors present on the surface of the lumen of BBB cells. This means of transport allows larger molecules to be able to reach the CNS, as is the case of low-density lipoproteins (LDL), insulin, angiotensin II, transferrin, and folates [34, 35]. There is still adsorption-mediated transcytosis, which occurs with albumin and immunoglobulin. Due to the anionic charge existing in the plasmatic membrane of endothelial cells, they will be able to interact with polycationic substances thanks to the electrostatic effect, and, thus, these molecules will be able to transpose the BBB [34, 35]. A different way for drugs to use these transport mechanisms will be, for example, mimicking endogenous nutrients and compounds. However, it is vital that they have certain characteristics for this to occur. In addition to the nanometric size to be displayed, these molecules should preferably have a high lipid solubility, in the range of 50–400 nm, and still not be substrates for active efflux transporters. Such requirements are crucial factors for transport to occur [50]. Nanoparticle systems are one of the most promising options for drugs to reach the CNS, in sufficient concentration, to obtain the desired therapeutic effect. Colloidal systems present themselves as effective candidates to overcome existing barriers. These consist of molecular aggregates with sizes ranging from 1 to 1000 nm and where drugs can be adsorbed, encapsulated, or covalently linked and thus be able to transpose the BBB [34, 35].

7.5.5 Nanoparticles (NPs)

NPs are an example of this type of systems, thanks to their versatility, and can be formed by different polymers, such as poly(alkyl cyanoacrylate) (PACA), polylactic acid (PLA), or poly(n-butylcyanoacrylate) (PBCA) and glycolic acid, the latter

being some of the most used for this purpose. Nanoparticles are useful tools in the treatment of CNS diseases, due to their versatility of adaptation, through the functionalization of the wrapping membrane on the surface of the nanoparticle, linking functional groups to their surface, in order to give specificity, increasing the effectiveness of the bioactive molecule of plant origin that they incorporate, and attenuating possible side effects [1]. Due to their characteristics, they protect the delicate bioactive molecules from degradation, reduce "renal clearance," and increase their half-life in the bloodstream, in addition to allowing the control of release kinetics and also changing the speed of dissolution [78].

There are several mechanisms for NPs to be able to transpose BBB:

1. Through transcytosis or endocytosis, taking advantage of the transport mechanisms existing in endothelial cells, enabling the transport of NPs with the respective therapeutic content through these cells
2. Inhibiting the transmembrane efflux system (inhibiting the function of GpP that is in the brain capillaries, pumping the drugs back into the blood, limiting their access to the brain)
3. Opening the occlusion junctions between endothelial cells and thus allowing the entry of bioactive phytochemical molecules through them
4. Inducing a local toxic effect on the cerebral vasculature, responsible for a limited permeabilization of endothelial cells
5. Thanks to the solubilization of the lipids existing in the membrane of endothelial cells, using surfactants associated with NPs, which leads to the fluidization of the membrane, known for its surfactant effect

However, it is in the functionalization of the surface of the nanoparticles that the reason for the success of its transport to the CNS is found. Specific transport systems located in the BBB can be used as targets, through the conjugation of the NPs with a specific carrier, which will be detected by the existing receivers in the BBB. The modification of the NPs can be performed using different types of props or functional appendices, for example, insulin, transferrin, lactoferrin, and antibodies or surfactants such as polysorbate 80. The surfactant Polysorbate 80 adsorbs some plasma proteins, such as apolipoprotein E, allowing its recognition and binding with the low-density lipoprotein receptor-related protein (LPR) existing in endothelial cells. The use of cationic nanoparticles (e.g., chitosan) is a very attractive alternative to promote the passage of drugs through the BBB. This system combines the advantage of a lipid matrix with a hydrophilic coating. The matrix serves as a reservoir for hydrophobic drugs, and the cationic surface favors endocytosis. The positive charge on the surface of these nanoparticles allows to create an electrostatic attraction with the negative charges present in the plasma membrane of the endothelial cells, thus promoting the transcytosis of these nanoparticles. Nanoparticles can be made up of polymers, lipids, or a combination of both. In this way, we can divide them into different classes according to their elaboration. A study carried out with albumin nanoparticles corroborates its successful transport to the brain, when these are coated with ApoE, after intravenous administration [120].

Table 7.11, below, will exemplify some of the techniques exposed as well as the drugs that are already using nanotechnology to overlap the BBB and reach the brain.

In the 1990s of the last century, solid lipid nanoparticles (SLNs) were developed, a class of colloidal particles composed of lipids, with high "in vivo" stability and which remain in solid state at room and body temperature. Compared to liposomes and polymeric nanoparticles, SLNs have greater load capacity, greater stability, and less cytotoxicity, allow controlled drug release, and have a relatively low production cost. In addition, during its production, organic solvents are not used and are formulations capable of being stable for up to 3 years. The size of the SLN varies between 50 and 1000 nm, and they are composed of lipids dispersed in an aqueous solution of surfactant(s) and can incorporate mainly lipophilic compounds. New studies

Table 7.11 Examples of drugs delivered by applied nanotechnology and their advantages

Polymeric nanoparticles	Solid lipid nanoparticles (SLNs)	Lipid nanocapsules (LNCs)
Methotrexate The amount of drug reaching the brain and cerebrospinal fluid increases, especially with NP of reduced dimension (<100 nm)	Doxorubicin PEG2000-based stearic acid SLN allowed Increase in circulation time and accumulation in the brain	Doxorubicin PEG2000-based stearic acid SLN allowed Increase in circulation time and accumulation in the brain
Dalargine BHE penetration is 3 times higher with the use of NP	Paclitaxel Oral administration causes a threefold increase Higher concentration in plasma and at brain level By combining this system with RNA, it is possible to reduce the tumor growth	Paclitaxel Prolongation of half-life in the brain of 21 minutes for more than 5 hours with the use of LNCs Decreased tumor progression in mice
Temozolomide Polysorbate 80-coated PBCA NPs transpose BBB both in vitro and in vivo	Camptothecin Improvement of AUC (area under the curve in the bioavailability) when this drug was administered orally using SLN formulated with stearic acid	Liposomes Phenytoin Improvement in local action in the treatment of epilepsy
Dexamethasone *The inflammation of the glial cells was significantly reduced with PLGA1 NPs*	Melatonin Late onset and improvement of AUC (area under the curve)	Cisplatin Increase in drug concentration and promotion of cell death in the areas affected by the tumor
Nimodipine Higher levels reached the blood, liquid cerebrospinal fluid, and brain tissue in vivo		Amphotericin, micelles, morphine Increased amount of drug reaching the brain
Methotrexate dendrimers *Improved drug transport in glioma situations*	Nanocarrier-based drug	Antibody nanocarrier

Source adapted from: Gomes [39]

have been developed, and a new class of lipid nanoparticles has emerged, the drug-lipid conjugates (LDC), produced to overcome the limitations of SLN and NLC, especially their reduced hydrophilic drug loading capacity. These systems are composed of solid lipid particles resulting from the bond between the drug and a lipid, through the formation of a salt (using a fatty acid) or by covalent bonding (with esters or ethers). Lipid nanocapsules (LNCs) are characterized as a hybrid structure between polymeric nanoparticles and liposomes, with the advantage of being more stable and simpler to produce, based on the inversion of phases of an oil/water emulsion as a function of a temperature change. Its structure consists of a matrix of oily liquid triglycerides, surrounded by a cohesive surfactant interface. Generally, LNCs have a negatively charged surface due to phospholipid molecules. These classes of lipid nanoparticles can be used as vehicles for transporting drugs to the CNS for different purposes:

1. Stabilize molecules that may be unstable both at biological and physical-chemical levels.
2. Improve the bioavailability of the drug transported.
3. Increase the permeation of a drug through the BBB.

Stabilize unstable physical-chemical or biological molecules, such as many drugs used to treat diseases in the CNS, and phytochemicals, which also have reduced in vivo stability. Recently, SLNs have been tested as a suitable platform to stabilize camptothecin in transport to the brain [70]. In vitro studies have shown a profile of prolonged release in plasma, confirming the physical stability of the particles at physiological pH. Interestingly, SLNs altered the biodistribution profile of camptothecin in vivo, prolonging its retention time in the brain, leading to greater effectiveness in reaching the therapeutic target and causing an increase in the potential antitumor effect of this molecule. In addition, side effects have been reduced. It was then concluded that SLNs are capable of stabilizing certain types of labile molecules, which can undergo hydrolysis processes. Although some molecules are theoretically capable of crossing the BBB, there are several factors that hinder this transport [70]. Studies were carried out using clozapine, an antipsychotic drug with lipophilic properties and with reduced oral bioavailability, due to the first pass through the liver. These were incorporated into SLN, composed of different types of triglycerides, and it was possible to observe that the bioavailability of this drug increased by three to four times, through intraduodenal administration. Noscapine, for example, used to treat glioblastoma, has a very short plasma half-life and undergoes rapid elimination. Madan et al. developed SLN with polyethylene glycol stearate to incorporate this drug and compared its effectiveness with SLN without this type of modification [68]. It was observed that the plasma half-life increased 11 times in the modified SLN and 5 times in the unchanged SLN, when compared with the drug in solution [68]. In a recent study, NLC modified with tricaprine and tristearin were studied, where bromocriptine, a dopaminergic agonist used in the treatment of Parkinson's disease, was incorporated. This drug has a slow onset of action (1–2 hours) and a prolonged half-life (3–5 hours),

which explains its reduced potential to reduce dyskinesia when compared to L-DOPA. In this sense, its incorporation into NLC represents a strategy to obtain stable plasma levels and increase its half-life. Study carried out with rats, after intraperitoneal administration of these systems, in order to assess their action potential in the control of Parkinson's disease. The results showed a reduction in akinesia, with greater efficiency in the groups in which NLC was administered, compared to those who received free bromocriptine. Lipid nanoparticles can be used as carriers that will interact with the BBB, making it possible for drugs that are unable to cross this barrier to penetrate.

Although lipid nanoparticles are able to cross the BBB, the increase in drug concentration in the intended target remains very limited. Over the past few years, new approaches based on endogenous transport systems located in the BBB have been studied. For this, the nanotransporters must be reformulated. As previously discussed, coating the nanoparticles with polysorbate 80 is a strategy to increase the absorption of ApoE on their surface, thus facilitating the endocytosis of these systems for the brain. In one of these studies, Tween®80 was used to stabilize SLNs, used as vehicles for the transport of curcumin. This molecule is an antioxidant with a high potential to be used at the neurological level, as reported in the panels in the preceding tables. The observed value of AUC (area under the curve) was eight times higher than the drug administered in free form, which confirms the prolongation of circulation obtained when this system is used. The concentration reached in the brain was 30 times higher, compared to free curcumin. The effectiveness of this transport system is due to the small particle size, which manages to avoid the mechanism of first passage in the liver [52].

7.6 Neurodegenerative Diseases

Neurodegenerative diseases are very debilitating conditions that result from progressive degeneration and death of neurons. Resveratrol is a polyphenol, found in grapes, that increases the body's antioxidant defenses and decreases pro-inflammatory cytokines, helping to maintain homeostasis. However, its pharmacokinetic properties are not favorable "in vivo," with reduced solubility and chemical instability and being rapidly metabolized. As a consequence, resveratrol can hardly reach the brain. With the use of solid lipid nanoparticles (SLN), to transport resveratrol, as these transporters are able to overcome the problems of solubility and degradation of this molecule, thus allowing it to reach the brain in therapeutic concentrations. The SLNs were coated with ApoE, which enabled their recognition and binding to the LPRs existing in the endothelial cells, thus promoting the endocytosis of these nano-systems. The in vitro results of using these SLNs revealed a 1.8-fold increase in the permeability of resveratrol when ApoE is used to coat the nanoparticles. It was then concluded that the use of SLNs conjugated to ApoE may be a strategy for the transport of resveratrol to the CNS in the fight against neurodegenerative diseases. Despite the advances achieved in recent years in the treatment of these neurological diseases, a

greater effort is needed to make these systems effective in vivo and to reduce their unknown neurotoxicity. BBB's role is to protect the CNS from potential toxic and xenobiotic agents. Nutraceutical systems for oral administration should be studied, in order to overcome the problems related to the first hepatic passage and penetration, in therapeutic doses by BBB. Thus, achieving a regular supply of antioxidants of plant origin, with little or no side effects observed, high synergy with allopathic drugs and other natural substances of phytochemical origin.

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Chapter 8
Emergency Situations

Milena Carvalho Libardi, Guilherme Riccioppo Rodrigues, and Rui Kleber do Vale Martins Filho

Introduction

Dementia is an umbrella term for several diseases affecting memory and other cognitive domains, which occurs mainly in older people and causes a huge socioeconomic impact worldwide. It is estimated that 50 million people have dementia, and nearly 10 million new cases will be diagnosed every year. From these, Alzheimer's disease (AD) is the most common form of dementia, present in almost 2/3 of the cases [1].

AD patients cause high levels of caregiver stress, depending on disease stage as well as several acute complications, which may have atypical clinical manifestations due to the paucity of information caused by the patient's cognitive loss. Therefore, emergency services should be aware of the most common clinical conditions that can acutely affect a patient with Alzheimer's, together with their diagnostic and therapeutic peculiarities.

We organized this chapter focusing the main clinical conditions experienced by patients with AD in an emergency room. For practical and didactic purposes, we have divided the chapter into two large syndromic groups: (1) conditions that change mental state, in which we address delirium or acute confusional state, epilepsy, behavioral and psychological symptoms of dementias, and drug reactions, and (2) conditions that present with focal signs, where we reviewed the main characteristics of stroke and traumatic brain injury, mainly subdural hemorrhage, in this population.

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8.1 Acute Mental Changes in Alzheimer's Disease

8.1.1 Delirium in Alzheimer's Disease

Delirium, also known as acute confusional state (ACS), is a neuropsychiatric condition of acute onset (hours to days) and fluctuating symptoms, which predominantly affects the attention and level of consciousness [2, 3]. Such symptoms may be accompanied by alterations in other cognitive domains (memory, orientation, language, organization of abstract thinking), impairment in sleep-wake cycle, and a deficit of self-perception. Oscillations in the level of consciousness are characteristic, producing a phenotypic spectrum sometimes difficult to recognize [4].

One- to two-thirds of ACS cases eventually remain undiagnosed [5, 6], which calls for a systematic approach based on identifying predisposing conditions and treating whenever possible the main triggers involved in the process [7]. Overall, the incidence of ACS in the general community ranges from 0.4% to 2%. These numbers rise substantially (11–42%) among patients admitted to the emergency room, with 15–20% of elderly individuals meeting criteria for delirium at hospital admission [8, 9].

Dementia is a frequent predisposing factor for ACS, with an incidence of 25–75% [10]. The risk for developing delirium increases with advanced age, concomitant use of multiple medications (especially drugs with anticholinergic effects, sedative-hypnotics, and narcotics), clinical disorders, physical restraints, malnutrition, use of devices such as urinary catheters, frequent changes in the environment, hearing and visual deficits, and iatrogenic procedures [11].

The pathophysiology of ACS seems to involve several networks that work synergistically, which ultimately culminate in a deficit of production of critical neurotransmitters, disturbing the brain homeostasis and consequently its normal functioning.

The precipitating factors associated with ACS, mainly infectious processes in 40% of the cases, promote an aberrant proinflammatory state with release of cytokines, impairment of the blood-brain barrier, and imbalance in levels of acetylcholine, dopamine, norepinephrine, and serotonin in the nervous system. Furthermore, processes of direct neuronal injury, such as hypoxia and metabolic disorders, lead to a neurological dysfunctional state with a myriad of distinct clinical manifestations [12, 13].

ACS may present within a spectrum of a hypoactive state, with predominance of lethargy, drowsiness, and motor slowness (the most common, present in up to 71% of patients) and a hyperactive state, with preponderance of signs of psychomotor agitation, restlessness, hallucinations, delusions, and hypervigilance. A mixed state, in which symptoms of hyper- and hypoactivity occur concomitantly or alternately, is also described [14]. The typical clinical scenario is an attention disorder with impairment of consciousness, perceptive stimuli deficit, or even symptoms related to other areas of cognition not explained solely by a previous neurodegenerative disease [15].

Traditionally, the diagnosis of ACS is based on the DSM-V criteria (Table 8.1) [16] with the support of a series of bedside assessment scales. Among the most used, the Confusion Assessment Method (CAM) (Table 8.2) is a tool of easy application and accuracy above 90% [17]. Psychiatric diseases are important differential diagnosis as depressive or manic episodes can manifest symptoms seen in hypoactive or hyperactive forms of ACS. In general, in patients with psychiatric conditions, symptoms are not as fluctuating as ACS. Additionally, a normal electroencephalogram points against the presence of ACS. Lewy bodies dementia is another important differential diagnosis, which also has a significant cognitive fluctuation, though with an insidious onset and duration of years [7, 8].

About one-third of elderly patients hospitalized with an episode of ACS persisted confused up to 6 months after discharge, leading to higher mortality rates regardless of age, previous functional status, and presence of dementia [18]. In patients with AD, those who have an episode of ACS might never recover their baseline cognitive status, usually presenting a progression of the underlying disease three times faster compared to patients who never had delirium. This finding is also associated with increased rates of hospitalization, institutionalization, and death [19].

The best approach encompasses risk stratification for delirium with a focus on identifying predisposing, precipitating, and perpetuating factors. When properly applied, these measures can decrease the risk for delirium by 30–40%, improving the clinical outcome of these patients [7]. Strategies that have focused on the management of risk factors for delirium in hospitalized patients were able to reduce the incidence of events, although did not affect their severity and recurrence rate [7]. A meta-analysis has shown a reduction in the number of delirium cases as well as their severity with the implementation of a proactive geriatric assessment plus the prescription of haloperidol in prophylactic doses in elderly candidates for hip surgery

Table 8.1 DSM-V criteria for delirium (acute confusional state)

The presence of delirium requires all criteria to be met:
Disturbance in attention and awareness
Acute onset and fluctuating symptoms
At least one additional disturbance in cognition
Disturbances are not better explained by a preexisting dementia
Disturbances do not occur in the context of severely reduced level of arousal or coma
Evidence of an underlying organic cause or causes

Table 8.2 Confusion Assessment Method (CAM)

The presence of delirium requires features 1 and 2 and either 3 or 4:
1. Acute change in mental status with a fluctuating course
2. Inattention
3. Disorganized thinking
4. Decreased level of consciousness

[20]. These findings suggest that a multidisciplinary approach based on periodic evaluations and a targeted management of the common risk factors related to ACS can improve the morbidity associated with these episodes.

Non-pharmacological methods should always be implemented in the treatment of delirium. Measures like minimizing physical restriction in bed, maintaining eye contact, alleviating auditory and visual deficits, and using understandable and objective verbal instructions to communicate with patients are important in dealing with confused patients [7, 21]. In case of severe agitation and psychotic symptoms causing risk to oneself or others, complementary pharmacological treatment based on typical and atypical antipsychotics is advised (Table 8.3) [7]. Particularly in AD patients, the adverse events (especially extrapyramidal effects) and the increased cardiovascular risk associated with the continued use of these medications should always be kept in mind [22, 23]. In general, when indicated, the American Psychiatric Association recommends the use of low doses of haloperidol in delusional patients. The atypical antipsychotics may be a reasonable alternative for those who do not tolerate or are not candidates for this drug [21].

8.1.2 Epileptic Seizures in Patients with Alzheimer's Disease

Neurogenerative diseases, together with stroke, traumatic brain injury (TBI) and brain tumors, are one of the main etiologies of epilepsy in patients older than 60 years [24]. Particularly in AD patients, there is an increased risk of epilepsy when compared to patients of the same age group [25]. In fact, AD and epilepsy seems to present an intrinsic relationship, where diagnostic and pathophysiological factors, prognostic implications, and particularities regarding the therapeutic management in this subgroup of patients should be carefully addressed [26].

The exact frequency of epilepsy in AD patients is not well established, but studies have shown a 5- to 10-fold increased risk for AD patients to develop epilepsy across the course of the disease, usually after an average of 6 years from the disease onset [27, 28]. The difficulty in estimating the real incidence of epileptic seizures in this population is explained, in part, by the complexity of recognizing subtle and subjective clinical manifestations characteristic of dyscognitive seizures, which eventually are attributed to other conditions, for example, behavioral changes related to the disease, syncope, drug effects, sleep periodic movements, etc. This phenomenon may explain the fact that contrary to what is observed in elderly patients in general, in whom partial seizures are preponderant, some studies indicate that generalized seizures are the most common manifestation in patients with AD. We presume these events are in most cases secondarily generalized episodes that have not been diagnosed earlier [27]. Of note, patients with genetic forms of AD (poor example caused by mutations in the *presenilin 1* gene) are at increased risk of epilepsy [29].

Based on experimental models in animals with expressed mutation in the *Amyloid Precursor Protein* gene, certain excitatory neural systems can be activated with β-amyloid accumulation, propagating interictal discharges and accelerating the pathological process of the disease [26]. In fact, a study carried out by Cretin et al. identified a subgroup of patients with AD who manifested temporal epileptic seizures in the prodromal phase of the disease, suggesting that early pathological changes observed in this condition may affect mesial limbic structures and precipitate epileptic seizures [30].

The management of AD patients with epilepsy should be primarily based on the education of caregivers and family members for early recognition of manifestations suggestive of ictal events. This measure can avoid subsequent seizures complications (e.g., falls, cognitive impairment, intracranial hemorrhages) and facilitate the diagnosis. On the other hand, the physician should be aware of the particularities of these patients, for example, lower renal filtration rate, decreased liver metabolism, use of psychotropic drugs interacting with antiepileptic drugs, decreased albumin levels, and changes in the distribution of fat tissue. Such considerations will be essential for the therapeutic plan and optimization of antiseizure therapy when indicated [26, 27].

In the emergency room, one must look for subtle signs suggestive of partial crises in the clinical history as manual or orofacial automatisms or transient impairment of the consciousness. In addition, such patients must undergo a neurological examination in search for focal signs that may suggest other concomitant neurological disorder (stroke, intracranial hematoma) or Todd's palsy. In addition, laboratory tests must be performed to rule out metabolic or infectious disorders capable of triggering acute symptomatic seizures. Neuroimaging and electroencephalogram (EEG) are useful to stratify the risk of recurrence, detect structural lesions, and diagnose status epilepticus in patients with persistent neurological dysfunction.

Therapy with antiepileptic drugs should be indicated in patients with at least two unprovoked seizures or in those at high risk of a second seizure, namely, patients with focal deficit, epileptiform changes in the EEG, and the presence of epileptogenic lesions on neuroimaging [31]. Due to the distinct characteristics of this subgroup of patients, the use of monotherapy at the lowest possible dose is the best option. Patients should receive drugs with less adverse effects on cognition, fewer drug interactions, less protein binding, and with good efficacy [32]. In this scenario, second-generation antiseizure drugs, especially levetiracetam and lamotrigine, appear as the most interesting alternatives, based on studies that demonstrated a lower cognitive effect (in some cases, such medications were associated with mild cognitive improvement or depression), good compliance, and high efficacy [26].

Finally, it is necessary to evaluate possible interactions and theoretical proconvulsant effects of some commonly prescribed drugs for AD patients. While the results related to the proconvulsant effect of the acetylcholinesterase inhibitors are quite controversial, some psychoactive drugs are known to decrease the seizure threshold [33, 34]. Among the antipsychotics, clozapine and chlorpromazine stand

out as medications frequently associated with seizures. Haloperidol, olanzapine, and quetiapine show an intermediate risk, whereas risperidone appears to have a safer profile. Between antidepressants, the tricyclics (especially clomipramine) and bupropion are the most associated with epileptic events [35, 36] (Box 8.1).

Box 8.1 Summary of the Main Aspects and Measures in the Approach of Patients with AD and Seizures

- Use an intravenous drug (benzodiazepines) to manage acute events. In case of persistence of symptoms for more than 5 min, treat for status epilepticus with other intravenous options.
- Pay attention to the presence of subtle manifestations of partial seizures in the clinical history. The presence of localizing signs on neurological exam may suggest complications arising from the seizure or concomitant affections (TBI, stroke, brain tumors).
- Perform blood tests looking for metabolic disorders or infection that may trigger an acute symptomatic seizure.
- Neuroimaging and electroencephalogram should be performed to stratify the risk of recurrence and rule out structural lesions. Patients with epileptogenic lesions on MRI or discharges on EEG should be treated with antiseizure therapy after the first episode.
- Prioritize second-generation drugs when indicated, seeking to combine efficacy, better profile of adverse events, and a low rate of drug interactions.

8.1.3 Behavioral and Psychological Symptoms of Dementia

Most patients with Alzheimer's disease (AD) will experience psychological and behavioral symptoms (BPSD) at some point in the course of the disease [37]. They are associated with a great impact on the quality of life of patients and caregivers, as well as a greater risk of institutionalization [38]. These symptoms can be classified into some main manifestations, such as depression, apathy, irritability, anxiety, euphoria, aggression, psychomotor agitation, delusions, hallucinations, sleep disturbances, and eating disorders [39]. For the scope of this chapter, we will discuss in detail three types of manifestations observed in an emergency department: agitation/aggression, psychosis, and depression.

Agitation/Aggression

Episodes of agitation and aggressive behavior occur in about 30% of dementia patients, and in almost half of patients, these events are severe [37]. Agitation can manifest as restlessness of variable intensity and, eventually, as aggressiveness, which can be verbal, with insults, cursing, or shouting, and physical, with hitting, biting, or throwing objects. An initial approach to patients with agitation should

seek to eliminate the triggering factor. In complicated cases, with risk of self- or hetero-aggression, a pharmacological intervention is necessary. Studies with typical antipsychotics such as haloperidol [40] and atypical antipsychotics such as risperidone [41] and aripiprazole [42] show efficacy on behavioral control. However, antipsychotics are associated with sedation, weight gain, extrapyramidal symptoms, QT interval prolongation, increased risk of cerebrovascular disease, cognitive deterioration, and increased mortality. Therefore, antipsychotics should be preferably discontinued within 12 weeks [23, 43]. Other pharmacological options, indicated for less severe cases or for long-term management of these patients, include memantine [44], antidepressants such as sertraline [45] or citalopram [46], and anticonvulsants such as carbamazepine [47].

Psychosis

Psychotic symptoms are common in AD. In early disease stages, about 12% of patients have delusions and 3% hallucinate [48]. As disease progresses, more than 50% of patients will experience psychotic symptoms, often persistent [49].

The approach to a patient with psychosis initially requires identification of the triggering factor, including investigation for delirium. In AD patients, the use of cholinesterase inhibitors [50] or memantine [44] can improve psychotic symptoms. If necessary, pharmacological treatment may include the use of atypical antipsychotics such as risperidone [23] and aripiprazole [42]. Again, long-term use of antipsychotics is associated with extrapyramidal side effects, accentuated cognitive decline, and increased mortality [51], so these medications should be kept for the shortest time possible. Recently, FDA approved pimavanserin, a new serotonergic (5-HT2A) antagonist with no muscarinic, antidopaminergic, or antihistaminic activity, for Parkinson disease-related psychosis. Pimavanserin has demonstrated efficacy in the treatment of AD-related psychosis in a phase 2 study [52]. However, pimavanserin has not yet been approved for clinical use in AD, and a potential increased risk of death is under investigation [53]. Table 8.3 shows the main atypical antipsychotics indicated for patients with AD.

Depression

Depression is a common condition in AD, occurring in almost 40% of patients [54]. Depression may be less severe and more fluctuating than in patients with intact cognition. There is also less suicidal ideation, less melancholy, and more motivational symptoms such as fatigue and apathy. The diagnosis of depression in individuals without dementia is highly dependent on their ability to report depressive symptoms such as worsening mood, loss of interest, hopelessness, and low self-esteem. In individuals with AD, language and capacity of expression is often impaired; therefore, it is necessary to detect the behavioral equivalents of a depressive episode, such as social isolation, irritability, or reduction of positive affect or pleasure in response to social contact or usual activities [55].

Effective treatment can improve affective symptoms, as well as cognition and other behavioral changes [43]. The use of Selective Serotonin Reuptake Inhibitors (SSRIs) has good tolerability and efficacy [56, 57] and should be prioritized over tricyclics or other drugs with anticholinergic effects.

Table 8.3 Atypical antipsychotics

Drug name	Dosing	Warnings
Aripiprazole	5–30 mg once daily *Increments of 5 mg every week if necessary	Severe cardiovascular disease Parkinson disease Presence of seizures Orthostatic hypotension
Olanzapine	2.5–10 mg once daily *Increments of 2.5 mg every 2 weeks if necessary	Severe cardiovascular disease Parkinson disease Presence of seizures Hepatic impairment Orthostatic hypotension
Quetiapine	25–400 mg/day ER: 1 or 2 times a day IR: 2 or 3 times a day *Increments of 25 mg every day if necessary	Presence of seizures Hepatic impairment
Risperidone	0.5–6 mg once or twice daily *Increments of 1 mg every day if necessary	Severe cardiovascular disease Parkinson disease Presence of seizures Hepatic impairment Renal impairment

*Can be adjusted according to the manufacturer's recommendation

Suicidal ideation, completed suicides, and suicide attempts are rare in AD patients. The risk factors are presence of insight into the diagnosis, depressive symptoms, male gender, high level of education, and history of previous suicide attempts [58]. Therefore, it is essential to be aware of these factors in patients with AD and develop treatment and support strategies in the most severe cases. Table 8.4 shows the main antidepressants indicated for patients with AD.

8.1.4 Drug Reactions

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare condition mainly associated with initiation or increase in the dose of antipsychotic medications [59]. In general, patients are prostrate with altered mental status, muscle rigidity, and fever. Body temperature can become very high, and there are also signs of sympathetic activation such as tachycardia, arterial hypertension, and diaphoresis [60]. Laboratory changes are mainly related to dehydration and muscle damage due to sustained contraction, with an increase in creatine phosphokinase (CPK) in approximately 70% of cases [61]. NMS usually persists for 7–14 days; however, it can last for up to a month [60]. The main differential diagnosis are infections, autoimmune encephalitis, malignant catatonia, and serotonin syndrome (SS) [61]. Table 8.5 describes the diagnostic criteria for NMS.

The treatment of NMS is predominantly based on discontinuing antipsychotic medication and rigorous intravenous hydration to prevent kidney damage from

Table 8.4 Antidepressant drugs

Drug name	Dosing	Warnings
Fluoxetine	10–80 mg once daily *Increments of 10–20 mg every week if necessary	Hepatic impairment Renal impairment Presence of seizures QT prolongation Strong inhibition of CYP2D6
Sertraline	25–200 mg once daily *Increments of 25–50 mg every week if necessary	Hepatic impairment Presence of seizures QT prolongation
Citalopram	10–40 mg once daily 10–20 mg (≥60 years of age) *Increments of 10 mg every week if necessary	Hepatic impairment Renal impairment Presence of seizures QT prolongation
Escitalopram	5–20 mg once daily *Increments of 5 mg every week if necessary	Hepatic impairment Renal impairment Presence of seizures
Bupropion	150–300 mg once daily (ER) or twice daily (IR) *Increments of 150 mg every week if necessary	Hypertension Hepatic impairment Renal impairment Presence of seizures
Mirtazapine	15–45 mg once daily *Increments of 15 mg every week if necessary	QT prolongation Weight gain Hepatic impairment Renal impairment Presence of seizures
Venlafaxine	37.5–225 mg once daily (ER) or twice daily (IR) *Increments of 75 mg every week if necessary	Hypertension Hepatic impairment Renal impairment Presence of seizures Hyponatremia
Desvenlafaxine	50–100 mg once daily *Increments of 50 mg every week if necessary	Hypertension Hepatic impairment Renal impairment Presence of seizures Hyponatremia
Duloxetine	30–120 mg once daily *Increments of 30 mg every week if necessary	Hypertension Hepatic impairment Renal impairment Presence of seizures Orthostatic hypotension Moderate inhibition of CYP2D6

*Can be adjusted according to the manufacturer's recommendation
IR Immediate release, *ER* extended release

rhabdomyolysis. If necessary, benzodiazepines, dopamine agonists, or dantrolene can be added (Fig. 8.1). It is important to note that bromocriptine can worsen cases of SS and should not be used if the diagnosis is uncertain. In cases that are refractory to the above measures, sedation with neuromuscular blockade and, finally, electroconvulsive therapy may be considered [62].

Table 8.5 Neuroleptic malignant syndrome criteria (Levenson 1985)

Major criteria
Fever
Rigidity
Elevated creatine phosphokinase levels
Minor criteria
Tachycardia
Abnormal blood pressure
Tachypnea
Altered consciousness
Diaphoresis
Leukocytosis

The presence of all three major, or two major and four minor, indicates a high probability of neuroleptic malignant syndrome

Serotonin Syndrome (SS)

There is about 10 mg of serotonin (5-hydroxytryptamine/5-HT) in the human body, near 4–8 mg in the enterochromaffin cells of the gastric and intestinal mucosa and the rest in platelets and the CNS. Serotonin is removed from the synaptic cleft via reuptake pumps or degraded by monoamine oxidase A (MAO-A) [63]. SS is caused by an excess of serotonin in the synaptic cleft, usually triggered by the use of therapeutic or supratherapeutic doses of antidepressants (monoamine oxidase inhibitors (MAOIs), SSRIs, tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors), opioid analgesics, triptans, antiemetics, or antimicrobials such as linezolid [64]. The symptoms manifest quickly, occurring in 50% of cases within 2 h after the use of medication, and are characterized in milder cases by irritability, tremors, and diarrhea. In more severe cases, they manifest with signs of neuromuscular hyperexcitability (e.g., tremor, myoclonus, hyperreflexia, hypertonia), dysautonomia (e.g., mydriasis, hypertension, tachycardia, dyspnea, hyperthermia), and altered mental status (e.g., confusion, agitation, hallucinations) [63]. The diagnostic criteria for SS are described on Table 8.6. The differential diagnosis to NMS is based on the faster onset and the presence of hyperreflexia and myoclonus predominantly in the lower limbs. The occurrence of mydriasis may also suggest the diagnosis of SS.

The treatment of SS should start with immediate discontinuation of all medications with serotonergic effect. Supportive treatment should be carried out with intravenous hydration, external cooling if hyperthermia, and benzodiazepines if agitation. Cyproheptadine, an antihistamine medication with an antiserotoninergic effect, can be used in patients who are able to receive medications orally or enterally. Initial dose is 12 mg, followed by 2 mg every 2 h until clinical improvement. In general, doses greater than 18 mg/day should not be used. An alternative for patients without conditions for enteral administration is the use of chlorpromazine or other antipsychotics that block 5HT2A receptors. In cases where there is diagnostic doubt concerning NMS, the use of antipsychotics can worsen the condition. In severe and refractory cases, sedation and neuromuscular blockade with non-depolarizing agents may be necessary [65].

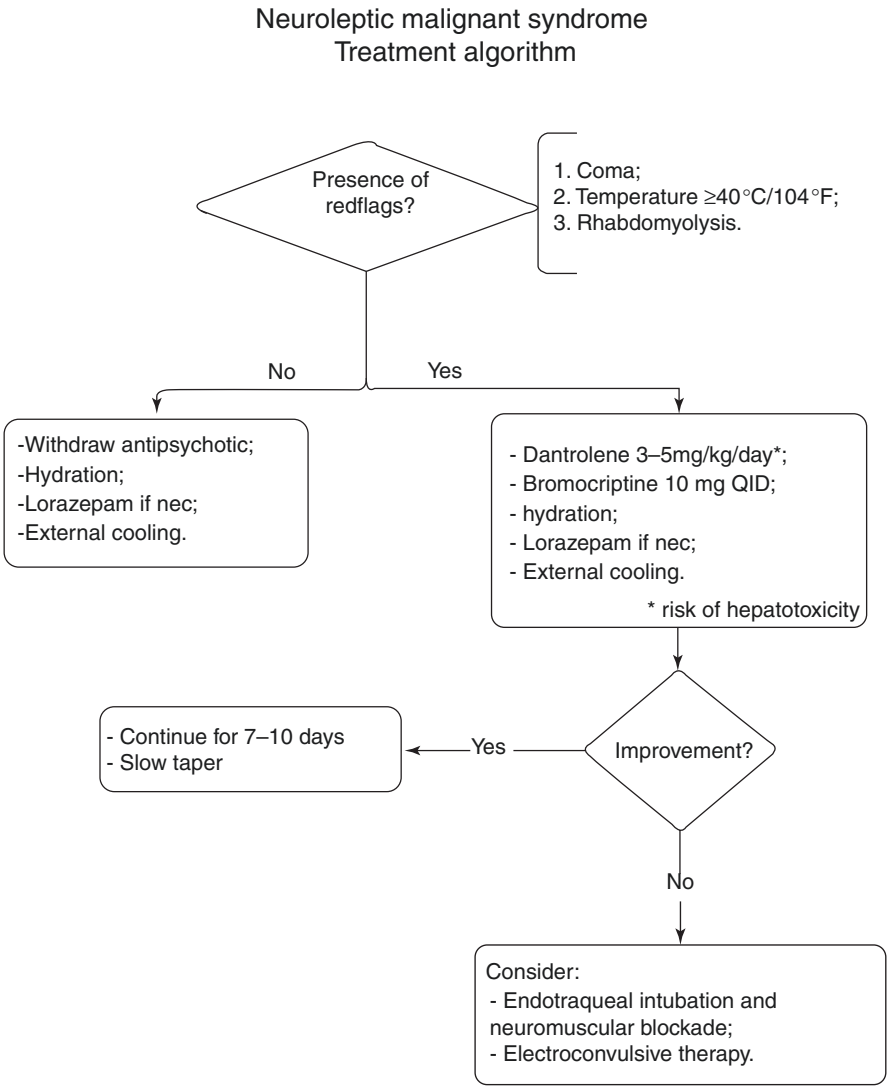

Fig. 8.1 Neuroleptic malignant syndrome treatment algorithm

Table 8.6 Hunter Serotonin Toxicity Criteria: decision rules for serotonin syndrome (Dunkley et al. 2003)

In the presence of a serotonergic agent, at least one is required:
1. Spontaneous clonus
2. Inducible clonus AND [agitation OR diaphoresis]
3. Ocular clonus AND [agitation OR diaphoresis]
4. Tremor AND hyperreflexia
5. Hypertonic AND temperature >38 °C AND [ocular clonus OR inducible clonus]

8.2 Acute Motor Deficits in Alzheimer's Disease

8.2.1 Stroke and Stroke Mimics in Alzheimer's Disease

Stroke and transient ischemic attack (TIA) are some of the most common emergency situations that we deal with in clinical practice, with patients at any age group, and this is not different with AD patients. Stroke is considered a life-changing event which affects dramatically the survivors and their family with a considerable impact on health system costs. According to the World Health Organization (WHO), stroke was the main cause of death and disability worldwide in 2019 and, along with heart disease, diabetes, lung cancer, and chronic obstructive pulmonary disease, was responsible for nearly 100 million additional healthy life-years lost in 2019 [66].

Previous studies have shown that hypertension, hypotension, heart failure, stroke, and coronary artery disease may worsen the cognitive decline in AD patients [67–69]. In addition, there is an association between AD and stroke because of excessive β-amyloid formation and oxidative stress, notably in the cerebral amyloid angiopathy (CAA) (Figs. 8.2 and 8.3). This condition causes lobar hemorrhagic strokes due to capillary fragility linked to β-amyloid peptide deposit around the brain microvasculature. Box 8.2 summarizes the relation between CAA and AD [67, 70].

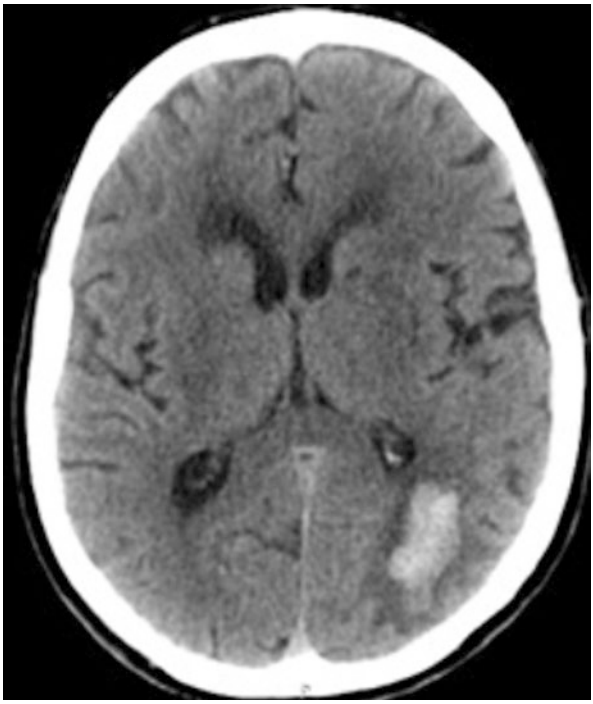

Fig. 8.2 (left) shows a non-contrast CT with cortical-subcortical hemorrhagic stroke in temporoparietal area in a 68-year-old female patient who did not have previous arterial hypertension but with initial AD at the presentation in emergency room

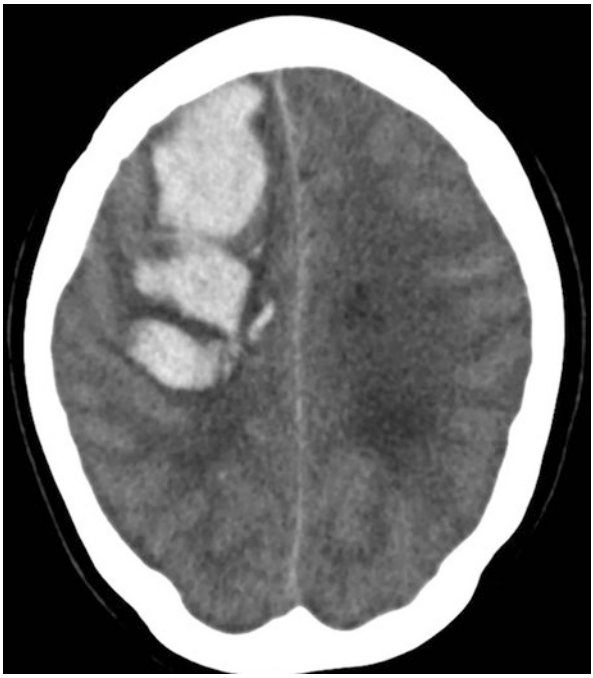

Fig. 8.3 (right) shows another 68-year-old male patient with a frontal lobe hemorrhagic stroke with an important blood heterogeneous volume content without risk factors for stroke but a cognitive decline 2 years before the stroke without investigation for AD. Both images according to Boston Criteria are likely CAA (Knudsen et al. 2001). These images and cases were provided by Dr. Libardi M personal archive

Box 8.2 Cerebral Amyloid Angiopathy and Alzheimer's Disease

1. Amyloid deposition is frequent in Alzheimer's disease, both in the center of senile or neuritic plaques and in vessel walls.
2. Dementia may precede cerebral hemorrhage from amyloid angiopathy.
3. Senile plaques are required to numerous in amyloid angiopathy and are accompanied by neurofibrillary changes.

   Important: However, remember that patients with amyloid angiopathy are not always symptomatic, nor is AD invariably demonstrable at autopsy.

   Prognosis: There is no treatment for amyloid angiopathy. Patients are susceptible to relapses of hemorrhages and strokes.

Cerebrovascular diseases can cause dementia, in isolation as vascular dementia, or in combination with AD as mixed dementia. Several previous cohorts [71–75] have demonstrated that this condition is highly prevalent in clinical practice due to the increase of risk factors described in Box 8.3. The overlap of findings in neuroimaging for cortical atrophy in AD and infarcts (symptomatic or not) increases the risk of mixed dementia as shown in the Baltimore Longitudinal Study of Aging [72].

Box 8.3 Risk Factors for a Stroke

1. Hypertension
2. Cardiomyopathy and atrial fibrillations
3. Diabetes
4. Obesity
5. Dyslipidemia
6. Diet and nutrition
7. Cigarette smoking
8. Alcohol consumption
9. Physical inactivity
10. Obstructive sleep apnea
11. Atherosclerosis[a]

[a]Aortic, carotid disease, vertebrobasilar disease, and intracranial atherosclerosis

Box 8.4 Signals and Symptoms of Stroke

- Sudden numbness or weakness in the face, arm, or leg, especially on one side of the body
- Sudden confusion, trouble speaking, or difficulty understanding speech
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance, or lack of coordination
- Sudden severe headache with no known cause

The occurrence of a sudden neurological deficit is the main clinical characteristic of a stroke. For caregivers and family members who live together with AD patients, depending on the severity of their cognitive impairment, it may be difficult to differentiate the clinical spectrum of many stroke types from nonurgent mimic conditions. In general, motor deficits and abrupt language changes or slurred speech are important warnings to take these patients to an emergency department. Box 8.4 shows the neurological deficits that usually occur in stroke. There are no clinical differences between ischemic or hemorrhagic stroke, and just an initial non-contrast computerized tomography (CT) can reveal the diagnosis. A CT performed in the first hours of an ischemic stroke generally does not show any evidence of alteration or may present only early signs of edema, such as loss of cortico-subcortical differentiation and sulcal effacement.

Besides stroke, the main causes of sudden neurological focal deficits are TIA and stroke mimics. In TIA, the deficit is reversible within 24 h, with complete recovery, and the patient does not have alteration on serial neuroimaging even into 48 h after onset. TIA must have the same clinical approach than stroke, including its

etiological investigation. Stroke mimics are conditions that can simulate a stroke. In elderly patients with cognitive impairment, these mimics are very common and can be caused by several disorders like electrolyte disturbances, hypoglycemia, epilepsy, or systemic infections [76].

AD patients with suspected stroke should be accompanied to emergency department for clinical evaluation. In clinical practice, a stroke in AD patients will initially have the same approach than patients with normal cognition. The treatment might be then individualized according to dementia severity and previous functional status. The main objective is warranting the best quality of life and functionality after a stroke. The decision in emergency room is a multidisciplinary responsibility, and the trinomial physician-patient-caregiver is very important and fundamental for a successful management in AD patients who have a stroke. This is the general approach suggested by the AHA/ASA and Canadian Society guidelines [77, 78].

When we are faced with a stroke diagnosis in clinical practice, it is important to consider that 80–85% of cases will be an ischemic stroke. Based on previous trials published since the NINDS and ECASS-3 trials in the 1990s, the acute ischemic stroke (AIS) gained an important advance on treatment, causing a huge impact for patients as well as in the health system scenario globally. Since then, patients around the world can be treated with alteplase until 4.5 h respecting the safety indications and contraindications. Patients with AD can be treated in case of AIS, and there are no contraindications if the neurological deficit will impact quality of life of those patients. Obviously, advanced AD should be taken into account when considering treating since alteplase may have more risks than benefits in such cases. The treatment of AIS with alteplase has a small rate of complications, and the principal occurrence is systemic bleeding [79–81]. Regarding elderly patients described in these main studies, when the scale is dichotomized for patients under 80 years of age (i.e., great prognosis, Rankin 0 or 1, vs. poor prognosis, Rankin 2–6), there is still a consistent benefit from thrombolysis (OR 1.6; 95% CI 1.4–1.7). Mortality is also reduced in thrombolysed patients (OR 0.87; 95% CI 0.79–0.95). Among patients older than 80 years, thrombolysis was also associated with a more favorable outcome at 90 days on the Rankin Scale (OR 1.4; 95% CI 1.3–1.6), and thrombolysis increased chance for the best prognosis (Rankin 0 or 1) by 90% (OR 1.9; 95% CI 1.5–2.3). The incidence of symptomatic intracerebral hemorrhage was 2.5% among those older than 80 years and 1.9% among those younger than 80 years (OR 1.3; 95% CI 0.96–1.8; $p = 0.07$). The incidence of asymptomatic hemorrhage was significantly higher in the elderly undergoing thrombolysis (11.0% vs. 8.3%; $p < 0.001$). Even with these findings, the benefit of the thrombolysis is still higher than risks [81]. Table 8.7 shows the Modified Rankin Scale used as functional outcomes after a stroke.

Hemorrhagic stroke is defined as spontaneous presence of cerebral intraparenchymal hemorrhage (IH). In patients with AD, IH is often caused by arterial

Table 8.7 Modified Rankin Scale used on stroke studies trials to measure the functional outcomes (Quinn et al. 2009)

Modified Rankin Scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities despite some symptoms
2	Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities
3	Moderate disability. Requires some help but able to walk unassisted
4	Moderate severe disability. Unable to attend to own bodily needs without assistance and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

hypertension or cerebral amyloid angiopathy. In these cases, stroke have worse prognosis due to high mortality rates, especially in patients with advanced dementia. The main clinical treatment here is aggressive blood pressure control (systolic pressure $\leq$140 mmHg) because increased arterial pressure level is associated with hematoma expansion [82].

Several recent trials [83] have shown that AIS treatment can go beyond intravenous thrombolysis. For large vessel occlusion (LVO) in the anterior circulation, mechanical thrombectomy is available with excellent functional outcomes. There is no contraindication of this procedure in AD patients. Again, the decision for this treatment should be based on the previous AD stage and if there is a cerebral tissue with chance of recanalization and reperfusion (penumbra area). Due to the reserved prognostic in a patient who has an important functional decline, the more appropriate approach is the palliative care on patients with malign stroke that also lost the time to thrombectomy or have contraindication or limitations to this technique. If the previous functionality of the patient is good, the benefit of well-indicated radio intervention treatments in stroke overcomes the risks [77, 78].

The decision of early decompressive hemicraniectomy in AD patients with an extensive stroke can be difficult. This invasive therapy performed until 48 h has shown good outcomes and decreasing mortality according to previous studies among patients of 60 years of age or younger and with complete or subtotal space-occupying middle cerebral artery infarction [84, 85]. However, in Destiny II trial, which only included patients 61 years old or older, although the procedure improved mortality rates, the majority of survivors in surgery group had moderate to severe disability [86].

Finally, the algorithm disclosed in Fig. 8.4 shows the stroke treatment currently based on the best evidence-based practice. We conclude that this can also be used in clinical practice in AD patients, individualized according to the patient profile, the caregivers demands, and the motor-cognitive disabilities.

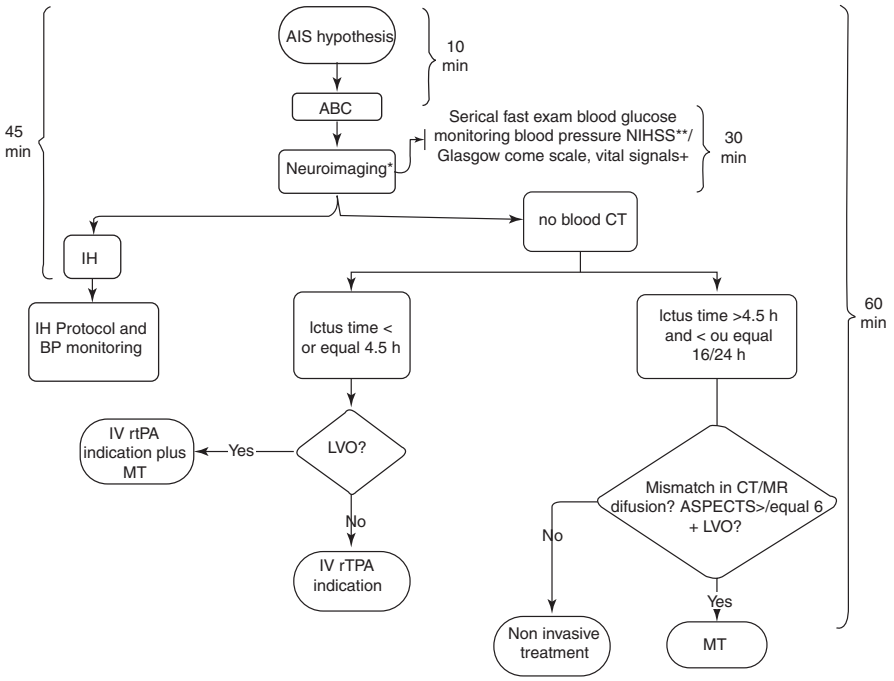

Fig. 8.4 Algorithm of acute stroke approach based on current guidelines. AIS: acute ischemic stroke. ABC: airway, breathing, circulation evaluation at admission on emergency room. *Neuroimaging: computerized tomography (CT) or magnetic resonance (MR). **NIHSS: NIH stroke scale. +vital signals: blood pressure, cardiac rate, O2 saturation, and respiratory frequency. IH: intraparenchymal hematoma or hemorrhage. BP: blood pressure. IV rtPA: intravenous alteplase drug. MT: mechanical thrombectomy. LVO: large vessel occlusion. ASPECTS: Alberta Stroke Program early CT score (Silva and Nogueira 2020)

8.2.2 Acute Subdural Hematoma and Other Acute Traumatic Brain Injury in Alzheimer's Disease

There are several cerebral lesions related to traumatic brain injury (TBI) in elderly patients, and the most common is acute subdural hematoma (aSDH). This injury carries a poor prognosis, and identifying those patients who may benefit from surgical intervention is essential to avoid a futile surgical intervention. The surgical treatment is generally indicated based on Glasgow Coma Score (Table 8.8), presence of focal deficits, and aSDH size and localization (Figs. 8.5 and 8.6). Additionally, the use of frailty scales can improve the prognostic definition of these cases, allowing to choose the best candidates for surgery [87].

Therefore, patients with advanced AD tend to receive conservative conduct (non-surgical approach) for TBI and aSDH and usually have more palliative care

Table 8.8 Glasgow Coma Scale

Glasgow Coma Scale		
Response	Scale	Score (points)
Eye opening response	Eyes open spontaneously.	4
	Eyes open to verbal command, speech, or shout.	3
	Eyes open to pain (not applied to face).	2
	No eye opening	1
Verbal response	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate response; words discernible	3
	Incomprehensible sounds or speech	2
	No verbal response	1
Motor response	Obey commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion and decorticate posture	3
	Extensor (rigid) response and decerebrate posture	2
	No motor response	1

Minor brain injury = 13–15 points, moderate brain injury = 9–12 points, severe brain injury = 3–8 points

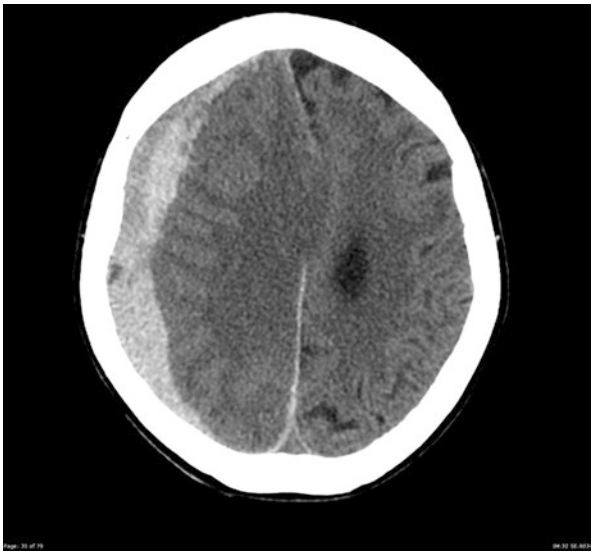

Fig. 8.5 Severe acute subdural hematoma in 72 years old patient with a previous dementia. This patient had taken oral anticoagulant plus had tripped on a step at home 4 days before admission at the hospital. He presented severe headache associated with a complete left motor deficit plus sudden drowsiness

indication independently of Glasgow and Marshall Score. Patients with initial AD can benefit from invasive treatments if they do not have other associated comorbidities, especially conditions related to coagulation disorders. Elderly patients using anticoagulants have more probability of hematoma expansion from aSDH or other

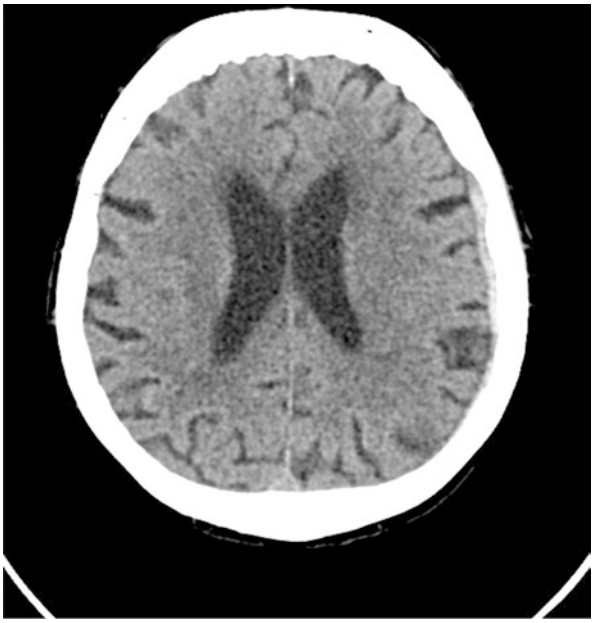

Fig. 8.6 Laminar acute subdural hematoma in 91 years old patient seen in left hemisphere. The cause of hematoma was by a low-impact motor vehicle accident where this patient was just the passenger

TBI. A recent trial showed benefit of prescribing tranexamic acid to prevent prolonged bleeding after trauma [88]. However, further studies are needed to define the value of this medication after TBI in the elderly.

It is important to emphasize that brain atrophy seen in dementia patients is able to accommodate a certain volume of blood from the aSDH. Many times, when the aSDH has a laminar aspect, the conservative management is recommended, and sequential non-contrast CT is indicated according to clinical evolution.

8.3 Conclusion

AD patients in emergency situations may not be able to contribute with a reliable medical history, so the medical team will have to rely on the help of their primary caregivers. We know that AD patients have a neurodegenerative disease, so it is mandatory to ensure the best quality of life and comfort for these patients, and these factors should be considered in the therapeutic choice. As mentioned in this chapter, there is a well-defined clinical approach for most clinical emergencies, but few studies have been done specifically with the population with dementia. Thus, every treatment should be individualized according to the stage of Alzheimer's disease in which the patient is.

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Chapter 9
Relationships Between Treatment and Clinical Evaluations

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9.1 The Laboratory Tests

Alzheimer's disease (AD) is a complex neurodegenerative disease that leads to progressive memory loss that mainly affects people over 60 years of age. It is one of the main causes of death in the world today. Given its heterogeneity and a still incomplete understanding of its pathology, biomarkers and targets available for therapy and its follow-up are still a challenge for an effective therapeutic strategy (Fig. 9.1). Several hypotheses have been proposed to understand the disease and identify markers and considered targets for treatments, and many studies have focused on finding effective blood biomarkers for accurate diagnosis of this disease; recent

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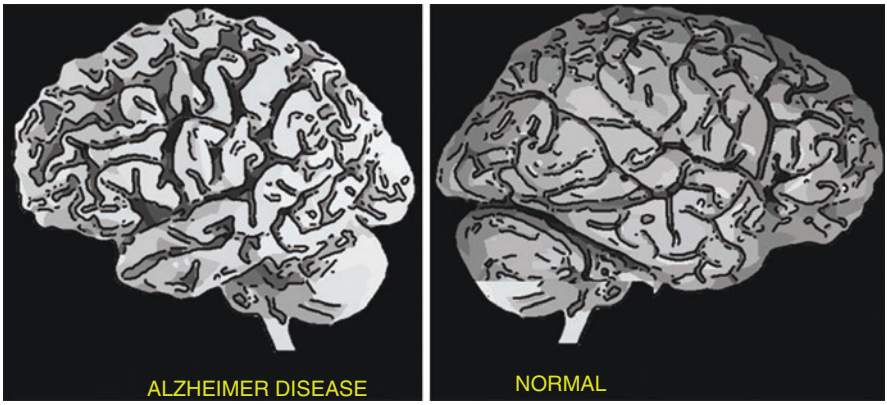

Fig. 9.1 Differences between normal and Alzheimer's brain. (Reference: Author personal)

studies demonstrate that four factors between regular blood checkups such as cortisol, highdensity lipoprotein triglyceride/cholesterol ratio, free alanine aminotransferase, and free triiodothyronine, indifference a difference or correlation with cerebral amyloid deposition [1–7].

As we know, individuals with cognitive impairment may have evidence of β-amyloid and tau protein biomarkers, but they will not necessarily develop clinical manifestations during their lifetime. Another point of interest is that the positive pattern of biomarkers in Alzheimer's disease can also be observed in other degenerative diseases, where we can observe that some pathologies of Alzheimer's disease are present as comorbidities. With this panorama, we can infer that there are still limitations and we need further studies of these biomarkers both for early diagnosis and to be able to monitor the development of the disease stages, thus helping to improve pharmacotherapy. With advances in molecular biology, we can analyze the diagnosis of Alzheimer's disease and focus on restricted groups of patients who have positive biomarkers along with specific Alzheimer's disease phenotypes, while individuals with cognitively uncompromised positive biomarkers should only be considered at risk for progression for Alzheimer's disease [8–10].

Another point of discussion is the monitoring of the treatment of Alzheimer's disease with the current pharmacotherapeutic arsenal, with the main drug groups interacting with some blood and urine biomarkers [9, 10].

The diagnostic tests currently available have shortened the early diagnosis of Alzheimer's disease; however, a definitive diagnosis is effective with the development of clinical dementia and, as mentioned, the finding of amyloid plaques and neurofibrillary tangles during necropsy [10–12].

A biomarker that would be ideal for monitoring the evolution of the disease, and even if the treatment proves to be effective in reducing cognitive effects or activities of daily living, needs to show clear criteria about the sensitivity of early diagnosis of Alzheimer's disease and its specificity, confirmed with the final result of the

necropsy, and must also have the ability to detect the disease at an early stage and to be able to monitor Alzheimer's disease and thus be able to monitor the therapeutic efficacy used [13–15].

In addition, laboratory tests of biomarkers found in CSF in Alzheimer's Disease (AD) may present difficulties in being routinely used for diagnostic screening of elderly patients, as we know that the invasiveness of lumbar puncture and the possible pre- and post-analytical difficulties resulting from handling, transport and other preanalyte factors can distort and consequently alter results, so the relationship between clinical treatment and some changes in laboratory results may occur due to the fluctuation of the circadian cycle of CSF components and biological fluids. As we know, many vital processes are affected by the circadian rhythm, which is the result of a set of endogenous biological events under the control of the suprachiasmatic nucleus. Thus, the circadian rhythm guarantees the maintenance of homeostasis, allowing the body to adapt to external stimuli, in which case false results may develop [1–3, 15, 16].

Taking into account the importance of circadian biology in regulating the health of the body, it can be inferred that any disruption of this system will have a negative impact on various physiological functions and will increase the susceptibility to various pathologies. In recent years, several studies have shown that the disturbance of the circadian rhythm is the origin of the neurodegenerative process of the disease, precedes cognitive decline, and contributes to its progress. This monograph explores the underlying mechanisms of circadian rhythm dysfunction and sleep-wake cycle changes related to the progression of Alzheimer's disease [16–21].

Although commonly associated with an abnormality of the brain, Alzheimer's Disease can also be characterized by a set of significant systemic changes with important changes associated with metabolic pathways, oxidative processes and inflammatory response, attacking tissues and systems, which prevents in many In cases of clarity in obtaining these results, we can already have several interferences, which has guided many researchers to investigate and develop assays of peripheral Alzheimer's disease (AD) biomarkers, with sensitivity and reliability with laboratory tests to identify early signs of Alzheimer's disease with minimally invasive skin samples and ultrasensitive biomarkers in blood and saliva [17–22].

Currently, among the most likely hypotheses to be the cause of Alzheimer's disease, the deposition of β-amyloid peptide in the cerebral cortex and hyperphosphorylation of tau protein are the most common. The diagnosis of Alzheimer's disease is based on the exclusion of other degenerative or systemic diseases and uses behavioral evaluations such as the clock tests, several questionnaires on the activity of daily living and cognitive functions, and imaging tests with special attention to computed tomography, magnetic resonance imaging, and nowadays the search for less invasive tests such as the collection of cerebrospinal fluid for tests where we can use the circulating blood and obtain an adequate and rapid prediction so that clinically a treatment can be initiated to reduce, maintain, and

improve the quality of life of the individual. Biotechnology has created very interesting methods for the early detection of Alzheimer's disease, by blood analysis, with special attention to platelets, hemoglobin, and vitamin B12; in recent studies can be evaluated the action of these respective markers showing that there were changes in patterns of hemoglobin and platelets of patients with AD when compared with healthy individuals and in relation to the parameters of vitamin B12. A decrease in levels was also observed in AD patients, showing that there may be a feasibility of using these blood biomarkers as predictive markers for the early diagnosis of Alzheimer's disease, because as we know some molecules recognized as biomarkers can be expressed in some body fluids. As can be seen in a recent study, there is a correlation between the variations in the concentrations of biomarkers t-Tau and Ab42 in the saliva of patients with confirmed AD and individuals in the inclusion group, but without AD, being that the expression of t-Tau in AD patients is significantly lower than in individuals without AD, while the salivary concentration of Ab42 is higher in AD patients, but not significantly different from that of the group without AD, which allows assessing that there is also the feasibility of using salivary biomarkers as predictive markers for the diagnosis of Alzheimer's disease (Table 9.1) [23–28].

Table 9.1 Laboratory tests for screening Alzheimer's disease

Blood	Biochemistry	Body fluids	Molecular biology	Imaging
CBC; erythrocyte sedimentation rate (ESR); blood glucose; platelets	Alkaline phosphatase; urea and creatinine; serum sodium, potassium, phosphorus, and calcium; proteinogram, glutamic-oxaloacetic transaminase (TGO); glutamic-pyruvic transaminase (TGP); gamma-glutamyl transferase (gamma-GT); syphilis; vitamin B12 and folic acid; free T4, TSH; serum drug dosage; HIV; vitamins B1 (thiamine) and B3 (niacin); heavy metal screening (zinc, copper, mercury, and manganese); tertiary infection by Borrelia-Lyme disease; disseminated lupus erythematosus (antinuclear antibodies and complement); gasometry; neoplastic markers; homocysteinemia	Urine I – quantitative sedimentation and culture Saliva Tears Feces CSF	ApoE: Préseniline 1 (PS1) Tau protein and AB42 Préseniline 2 (PS2)	Isotopic cisternography CT MRI PET/CT Digital radiology

Source: Author himself

9.1.1 Aspects of Treatment and Relationship with Laboratory Tests and Clinical Evolution of Alzheimer's Disease

The biomarkers total tau (T-tau), phosphorylated tau (P-tau), and β-amyloid (Aβ) in the cerebrospinal fluid (CSF) are currently considered particularly reliable. One of the reasons is that CSF directly interacts with the extracellular space in the brain and therefore reflects relevant biochemical and pathological factors, because both Aβ42 and tau (total tau and phosphorylated tau) are widely accepted as central cerebrospinal fluid biomarkers for the AD dementia diagnosis [4, 29, 30].

Although these biomarkers are very useful and are now included in the diagnostic criteria, they still have some limitations, such as inter-laboratory and intra-laboratory variability and large overlap with other forms of dementia [4].

The drugs currently used to treat Alzheimer's disease are donepezil, memantine, rivastigmine and etanercept. Its correlation with routine clinical and laboratory tests focusing on possible interferences of interest are described below:

Donepezil: Indicated in the symptomatic treatment of Alzheimer's disease of mild, moderately severe, and severe intensity; it should not be indicated for patients with hypersensitivity to donepezil hydrochloride, piperidine derivatives, or any excipient used in the formulation.

Donepezil is a cholinesterase inhibitor, which can exacerbate succinylcholine-like muscle relaxation during anesthesia, increase gastric acid secretion due to increased cholinergic activity, and have vagotonic effects on heart rate. It should be prescribed with caution to patients with a history of asthma. Has the potential to cause generalized seizures; however, this situation can also be a manifestation of Alzheimer's disease. Rare cases of neuroleptic malignant syndrome and rhabdomyolysis have been reported. Alzheimer's dementia can impair performance in the ability to drive a vehicle or operate machinery; in addition, donepezil may cause fatigue, dizziness and muscle cramps, especially when starting or increasing the dose.

It should only be used during pregnancy if the potential benefit justifies the potential risks to the fetus. There are no clear reports on the interference in laboratory tests of donepezil [5, 31, 32].

Memantine: This medicine is not an AChE inhibitor. Its function is to prevent the effects of an excessive amount of a chemical called glutamate in the brain. Memantine is used for moderate to severe Alzheimer's disease. It is suitable for people who cannot take or tolerate acetylcholinesterase inhibitors.

It is also suitable for patients with -already modifying Alzheimer's disease and ACh inhibitors. Incidents can include headache, side effects, and a lot of constipation, but are usually common. There are no reports of significant changes in laboratory tests. The most frequent adverse reactions are related to the head: dizziness, dizziness, pain, constipation, drowsiness, infection, phonic infections. Among the most common cynical effects are immune system disorders, psychiatric disorders and psychotic reactions, cardiac disorders, vasculopathies, venous thrombosis/

thromboembolism, hepatobiliary disorders, Alzheimer's disease (AD) and changes in liver function [33–35].

Rivastigmine: Rivastigmine tartrate, presented under the trade name Exelon®, is manufactured by the pharmaceutical laboratory Novartis Biosciences SA and was approved by the US Food and Drug Administration (FDA) in April 2000.

This drug has been shown to be an effective inhibitor of carbamate-type acetylcholinesterase enzyme, admitting, even though further studies are needed, that it facilitates cholinergic neurotransmission by delaying the degradation of acetylcholine released by functionally intact cholinergic neurons. Rivastigmine has a pseudo-irreversible inhibition mechanism, because in the interaction of the enzyme with rivastigmine, which occurs in the synaptic cleft, there is the formation of a phenolic cleavage product with minimal pharmacological activity and rapid excretion, in addition to a carbamylated complex with the enzyme, which prevents the hydrolysis of acetylcholine, by competitive and lasting but reversible inhibition.

The most common effects are dizziness, headache, nausea, vomiting, diarrhea, anorexia, fatigue, insomnia, confusion, and abdominal pain. Less commonly, depression, anxiety, drowsiness, hallucinations, syncope, hypertension, dyspepsia, constipation, flatulence, weight loss, urinary tract infection, weakness, tremor, angina, gastric or duodenal ulcer, and rash may occur. Anticholinergic agents can reduce its effects. Other significant interactions were not observed, which may alter serum urea and creatinine levels. Rivastigmine should be used with caution in patients with peptic ulcers, a history of seizures, changes in cardiac conduction, and asthma [36–39].

Galantamine: It is the most recent drug in the group of Acetylcholinesterase inhibitors (AChEIs), approved by the FDA in the United States and by ANVISA in Brazil in 2001. It is a phenanthrenic alkaloid that reversibly and competitively inhibits AChE, being also a nicotinic modulator. Studies that the prevalence of adverse effects and deaths were more common in the galantamine group than in the placebo group, however, claim that safety and tolerability was equivalent or superior to what is reported in trials for mild or moderate Alzheimer's disease when compared to trials of other cholinesterase inhibitors in patients in the severe stage of the disease [35, 40–42].

The treatments currently available, that is, acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and the N-methyl-d-aspartate receptor antagonist (memantine), contribute with minimal impact on the disease and target the late aspects of the disease. These drugs slow the progression of the disease, provide symptomatic relief, but fail to achieve a permanent cure.

Although the neuropathological features of Alzheimer's disease are recognized, the complexities of the mechanism have not been clearly defined.

This lack of understanding of the pathogenic process may be the likely reason for the unavailability of an effective treatment that can prevent the onset and progression of the disease. Due to important progress in the field of pathophysiology over the past 2 years, new therapeutic targets are available that should address the underlying disease process directly [35, 40–42].

9.1.2 Clinical-Laboratory Aspects

The basis of clinical assessment and treatment of Alzheimer's disease (AD) today must involve the indication of drugs, a deeper analysis of biochemical biomarkers and, above all, the use of non-drug therapies, based on psychotherapeutic care centered on the patient and with the interface between the doctor and his caregiver, creating a plan of care and risk management for this patient. The Food and Drug Administration (FDA) has approved the use of the combination of cholinesterase inhibitor drugs (ChEIs) and the N-methyl-d-aspartic acid (NMDA) antagonist memantine as part of a comprehensive treatment plan according to the guidelines. results obtained in systematic reviews. Although medications are generally considered symptomatic, they can provide a mild "disease-modifying" effect, improve cognition, and reduce loss of independence. When drugs and non-drug treatments are combined, they can significantly alleviate symptoms and reduce clinical progress and burden of care. Drug treatment for AD involves first identifying and eliminating potentially harmful drugs and supplements [43, 44].

The first-line treatment for neuropsychiatric symptoms and problem behaviors is non-pharmacological treatment, which involves psychological education, identification and implementation of triggers, iterative assessment, and adjustment of behavioral and environmental interventions. In-depth research work is underway to develop more accurate and practical AD diagnostic biomarkers and clinical tools, as well as better treatment methods. Studies involving the primary prevention of AD, associated with clinical trials with drug treatments to relieve symptoms, have sought several therapeutic targets that have an effective action with reduction of the pathological process involving the degeneration of Tau protein and the accumulation of amyloid beta pepithenium of mitochondrial alterations, action on glial cells, promoting a decrease or delay in neuropsychiatric symptoms and as a result of an improvement in the individual's quality of life in a multidisciplinary way: prevention and effective therapeutic drug action [45–48].

Alzheimer's disease (AD) care requires early diagnosis and multidisciplinary management. This assessment of AD should involve structured analysis of the patient's history with a focus on activity and quality of symptoms and laboratory tests (biochemical and diagnostic imaging) to determine the level of impairment, assess which cognitive-behavioral syndrome is and if possible diagnose its cause. Clinical biomarkers are available to aid in the etiologic diagnosis. The clinician's role in establishing shared goals and decision-making between patient and caregiver when psychotherapeutic actions can broadly assist and when combined, pharmacological and non-pharmacological therapies alleviate symptoms and reduce clinical progression and burden of care. care. The biopathological processes of AD develop over decades before symptoms appear; this period is being increasingly researched as an opportunity to improve the development of symptoms, delaying when possible or even preventing Alzheimer's disease (AD) through clinical evaluation of the multidisciplinary management of AD [49–52].

Recent research has suggested a potential association between certain infectious diseases and dementia, either directly due to bacterial invasion of the brain and toxin production or indirectly through modulation of the immune response. Therefore, in this review, we focus on emerging issues of bacterial infection and AD, including the existence of antimicrobial peptides with pore-forming properties that act similarly to Aβ-formed pores in a variety of cell membranes. Special focus is placed on oral bacteria and biofilms and the potential mechanisms that link bacterial infection and toxin production in AD. The role of bacterial outer membrane vesicles in the transport and delivery of toxins, as well as porins, to the brain is also discussed. Aβ has been shown to have antimicrobial activity against various bacteria and therefore could be upregulated in response to bacteria and bacterial toxins in the brain. Although more research is needed, we believe that controlling biofilm-mediated diseases may be an important potential prevention mechanism for the development of AD [53, 54].

The microorganisms residing in our bodies participate in a variety of regulatory and pathogenic processes. Here, we describe how the etiological pathways implicated in Alzheimer's disease (AD) can be regulated or disturbed by symbiotic microbial activity. Furthermore, the composition of symbiotic microbes has changed dramatically throughout human history, along with the rise of agriculturalism, industrialization, and globalization. We postulate that each of these lifestyle transitions engendered progressive depletion of microbial diversity and increased virulence, thus increasing AD risk pathways. Human life expectancy likely extended into the eighth decade, tens of thousands of years ago, but little is known about premodern geriatric epidemiology. We propose that the microbiota of the intestine, oral cavity, nasal cavity, and brain can modulate the pathogenesis of AD, and that changes in the microbial composition of these body regions throughout history suggest an increased risk of AD. Dysbiosis can promote immunoregulatory dysfunction due to inadequate education of the immune system, chronic inflammation, and permeability of the epithelial barrier. Subsequently, pro-inflammatory agents – and occasionally microbes – can infiltrate the brain and promote AD pathogenic processes. APOE genotypes appear to moderate the effect of dysbiosis on AD risk. Elucidating the effect of symbiotic microbiota on AD pathogenesis can contribute to basic and translational research [7, 55, 56].

The gut microbiota has a proven role in regulating several neurochemical pathways through the highly interconnected gut-brain axis. Oral bacteriotherapy, therefore, has potential in the treatment of pathologies related to the central nervous system, such as Alzheimer's disease (AD). Current AD treatments aim to prevent onset, delay progression, and improve symptoms. In this work, 3xTg-AD mice in early-stage AD were treated with the probiotic formulation SLAB51, thus affecting the composition of the intestinal microbiota and its metabolites. This influenced the plasma concentration of inflammatory cytokines and key metabolic hormones considered therapeutic targets in neurodegeneration [57, 58].

PKC signaling is critical for the non-toxic degradation of amyloid precursor protein (APP) and inhibition of GSK3beta, which controls tau protein phosphorylation in Alzheimer's disease (AD). Thus, poor regulation of PKC signaling may

contribute to the origins of AD. Bryostatin, a potent PKC modulator, has the potential to improve both neurodegeneration and recent memory loss associated with AD. As reported here, bryostatin and a potent synthetic analogue (picolog) are found to cause stimulation of non-amyloidogenic pathways, increasing alpha-secretase activity and thus decreasing the amount of toxic Abeta produced [59, 60].

Both bryostatin and picolog increased the secretion of the alpha-secretase product (s-APP-alpha) of APP at sub-nanomolar to nanomolar concentrations. A peripheral AD biomarker was previously validated by autopsy. This biomarker, based on the differential bradykinin-induced phosphorylation of Erk1 and Erk2, was used here to test therapeutic efficacy for both bryostatin and picolog. Both PKC activators are then shown to convert the AD Erk1/2 fibroblast phenotype into the "normal" control skin fibroblast phenotype. This conversion occurred both for the abnormal Erk1/2 phenotype induced by the application of Abeta (1-42) to fibroblasts and for the phenotype observed for fibroblasts from patients with AD. Abeta (1-42) induction and PKC modulator reversal of the AD biomarker Erk1/2 phenotype demonstrate the AD biomarker's potential to monitor disease progression and treatment response. In addition, this first demonstration of the therapeutic potential in AD of a synthetically accessible bryostatin analogue ensures further preclinical advancement [61, 62].

Neurological disorders have been found to influence peripheral tissues outside the CNS. Recent developments in CNS biomarkers have emerged with several diagnostic and therapeutic shortcomings. The role of central biomarkers including CSF-based probes and molecular imaging is still unclear for early diagnosis of major neurological diseases. Current trends show that early detection of neurodegenerative diseases with noninvasive methods is one of the main focuses of researchers, and the development of biomarkers targeting peripheral tissues is on the rise. Alzheimer's and Parkinson's diseases are known for the progressive loss of neural structures or functions, including neural death. Several dysfunctions of metabolic and biochemical pathways are associated with the early occurrence of neurodisorders in peripheral tissues, including skin, blood cells, and eyes. This article reviews peripheral biomarkers explored for early detection of Alzheimer's and Parkinson's diseases, including blood cells, skin fibroblasts, proteomics, saliva, olfactory, stomach and colon, heart, and peripheral nervous system [63, 64].

The accumulation of clinical research data supports that central cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) amyloid β (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau) reflect elements key to AD pathophysiology. Importantly, many clinical studies show quite consistently that these biomarkers contribute relevant diagnostic information, also in the early stages of the disease. Recent technical developments have made it possible to measure these biomarkers using fully automated assays with high precision and stability [65–67].

Standardization efforts provided certified reference materials for CSF Aβ42, with the aim of harmonizing results across assay formats that would allow for uniform global reference limits and cutoff values. These encouraging developments have led to central AD CSF biomarkers taking a central position in the new

diagnostic criteria for the disease and in the recent biological definition of AD by the National Institute on Aging and Alzheimer's Association.

Taken together, this progress will likely serve as the basis for a more general introduction of these diagnostic tests into routine clinical practice. However, the heterogeneity of pathology in late-onset AD requires an expansion of the CSF AD biomarker toolbox with additional biomarkers reflecting additional aspects of AD pathophysiology. A promising candidate is the synaptic protein neurogranin which appears specific for AD and predicts the future rate of cognitive deterioration. Furthermore, recent studies bring hope for easily accessible and cost-effective screening tools in the early diagnostic assessment of patients with cognitive impairment (and suspected AD) in primary care. In this regard, technical developments with ultrasensitive immunoassays and new mass spectrometry techniques promise biomarkers to monitor cerebral amyloidosis (the Aβ42/40 or APP669–711/Aβ42 ratios) and neurodegeneration (tau light proteins and neurofilament) in samples of plasma, but future studies are needed to further validate these promising results [68, 69].

We can observe then that the use of medications associated with the Alzheimer's disease clinic is a field of study at the moment with many questions and the search for clinical correlations that can be translated in the form of an algorithm, using sick patients and healthy patients in a collection of biological fluids and cellular material so that we can find answers in a not too distant time [68, 69].

9.2 Image

The combinatorial use of biomarkers derived from biological fluids, such as cerebrospinal fluid (CSF), with advanced molecular imaging and neuropsychological tests may eventually achieve the diagnostic sensitivity and specificity needed to identify people in the early stages of the disease, when drug modification is more likely possible. In this regard, positive retention of amyloid or tau tracer in positron emission tomography imaging, low concentrations of amyloid β 1-42 peptide, high concentrations of CSF in total tau and phospho-tau, mesial temporal lobe atrophy on MRI, and temporoparietal/precuneiform hypometabolism or hypoperfusion on positron emission tomography with 18F-fluorodeoxyglucose emerged as biomarkers for progression to AD.

However, the final panel of AD biomarkers will likely involve the inclusion of new biomarkers in CSF and blood more precisely associated with confirmed pathophysiological mechanisms to improve their reliability in detecting preclinical AD. This review highlights advances in biological fluid and imaging biomarkers that are moving the field toward the goal of preclinical detection of AD [70–73].

The brain is highly enriched in lipids, and intensive study of these lipids can be informative, not only about normal brain function but also about changes with age and disease. In recent years, the development of highly sensitive mass spectrometry platforms and other high-throughput technologies has enabled the discovery of

complex changes across the entire lipid. This lipidomic approach promises to be a particularly useful tool for identifying diagnostic biomarkers for the early detection of age-related neurodegenerative diseases such as Alzheimer's disease (AD), which until recently was limited to protein- and gene-centric approaches. This review highlights the known lipid changes that affect the AD brain and provides an update on the progress of research on lipid biomarkers in AD [73, 74].

Advances in functional brain imaging technology allow researchers to assess the brain in a non-invasive way so they can observe phenomena that would otherwise be impossible to analyze. For example, the advanced technique of magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) allow the characterization of the neural connection network and on the other hand, positron emission tomography (PET) allows the detection of a highaffinity molecular probe by picomolar concentrations for detection of amyloid concentrations in the brain, serving as a very early clinical guide for the patient [73–75].

β-Amyloid (Aβ) deposition and neurofibrillary tangles (NFT) with abnormal hyperphosphorylation of tau are the pathological hallmarks of the disease and are accompanied by other pathological processes, such as microglial activation. Imaging functional and molecular nuclear medicine using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) technology provides valuable insight into the underlying disease process years before clinical symptoms appear. Nuclear neuroimaging in AD has made great progress in the last 20 years and has surpassed the traditional role of brain perfusion and the assessment of glucose metabolism, and with this, radiopharmaceutical markers have led to the development of several probes capable of detecting Aβ deposition, tau protein accumulation, microglial activation, and neuroinflammation [2–8, 69, 76, 77].

9.3 Magnetic Resonance Imaging

Technologies for evaluating possible biomarkers of Alzheimer's Disease (AD) use magnetic resonance imaging and are currently focused on in vivo brain imaging with MRI and Amyloid PET, as well as biochemical assays in cerebrospinal fluid (CSF) and peripheral tissues. CSF biomarkers have received increased attention in the last decade. However, it is unclear whether these biomarkers are able to diagnose AD early, before the accumulation of amyloid beta, or whether they can differentiate between AD and non-AD dementias. In addition, CSF biomarkers may not be useful for diagnostic screening of elderly patients, given the invasiveness of lumbar puncture, laboratory variability in techniques and sample handling, and circadian fluctuation of cerebrospinal fluid (CSF) components [76, 77].

Although commonly seen as an abnormality of the brain, AD is a systemic disease with associated dysfunction in metabolic, oxidative, inflammatory, and biochemical pathways in peripheral tissues such as skin and blood cells. This has led researchers to investigate and develop peripheral AD biomarker assays (some with high sensitivity and specificity) that require minimally invasive skin or blood samples [74–77].

Positron emission tomography (PET) is a technique that allows the detection of metabolic alterations, through the use of radiopharmaceuticals, whose molecular structure is composed of a molecule analogous to glucose linked to a radioactive element, which is administered intravenously. or inhalation to the patient. Regions that metabolize excess glucose, such as tumors or brain regions in intense activity, are identified on scintigraphic images. Early signs of Alzheimer's in the pre-clinical phase, allowing the delay in the onset of limiting symptoms of the disease in the advanced phase. Studies show that only with the clinical examination, the percentage of certainty of the diagnosis of the pre-clinical phase is around 60% to 70%. In association with magnetic resonance, we can have a concentration of this material, but with the spatial and limited resolution in PET, the important contribution of MRI arises when combined with the acquisition of PET images, giving rise to the multimodal PET/MRI system that can provide information of interest, facilitating the identification of specific degenerative patterns of Parkinson's disease, multisystem atrophy, progressive supranuclear palsy, and corticobasal degeneration in addition to Alzheimer's Disease.

Combining PET and RM in a single unit that allows simultaneous acquisitions, while intuitively simple, is technically much more complex than it sounds. Traditional PET detectors and their associated electrical components, such as photomultiplier tubes (PM) responsible for converting the photon interaction signal into an electrical signal, do not adequately perform their functions in the presence of high magnetic fields. Therefore, one of the solutions regarding these adaptations and modifications of the systems was the development of a new PET detector technology compatible with magnetic fields, that is, detectors with silicon photomultipliers (SiPM), which enable greater detection sensitivity with greater flexibility of the PET/RM protocols.

There are currently four options for PET/RM equipment and three ways to integrate PET with RM [74–77]:

1. PET and RM equipment are independent and located in different rooms. The integration of images is performed by specialized programs, enabling routine flexibility in radiodiagnosis, as the systems can be used separately.
2. Sequential images are performed on different equipment.
3. By fully integrated systems, in which images are simultaneously acquired, with the patient on a single examination table and coupled equipment.

Thus, structural magnetic resonance imaging (RME) is based on anatomical measurements of the volume of the hippocampus, which is in accordance with memories and emotions. Aging leads to atrophy of the entire cerebral cortex, including the hippocampus; however, the decrease in volume has been attributed to neurodegenerative diseases. Measurement of hippocampal volume is now used as a biomarker for AD, in diagnosis and follow-up. Manually measured hippocampal volume is the gold standard for verifying automation measurements, although there is no standard for this in the Volume Measurement literature. Research on uniform volume measurement was carried out on a voluntary basis through the European

Alzheimer's Disease Consortium (EADC) and Alzheimer's Disease Neuroimaging Initiative (ADNI).

The volume of the hippocampus or medial temporal lobe, the most studied brain region, shows low sensitivity and specificity and is not eligible for structural magnetic resonance imaging as an independent complementary test for the early diagnosis of Alzheimer's disease in patients with CCL.

This is consistent with international guidelines, which recommend imaging tests to exclude non-degenerative or surgical causes of cognitive impairment rather than diagnosing dementia caused by Alzheimer's disease. Due to the low methodological quality of most of the included studies, the results of this review should be interpreted with caution. Future research should not focus on a single biomarker, but on a combination of biomarkers to improve early diagnosis of dementia caused by Alzheimer's disease [72–75].

We can conclude that patients with mild cognitive impairment (MCI) generally have more memory problems than their peers, but these problems are not severe enough to be classified as dementia. Studies have shown that people with CCL and memory loss are more likely to develop dementia due to Alzheimer's disease (approximately 10% to 15% of cases per year) compared to people without CCL (1% to 2% per year). Currently, the only reliable way to diagnose dementia caused by Alzheimer's disease is to follow patients with CCL and assess cognitive changes over the years. Magnetic resonance imaging (MRI) can detect the structural changes in the brain that indicate the onset of Alzheimer's disease. Early diagnosis of CCL caused by Alzheimer's disease is important because patients with CCL can benefit from early treatment to prevent or delay cognitive decline. Several biomarkers have been proposed for the early diagnosis and longitudinal monitoring of AD through imaging techniques, but all these biomarkers have their limitations in terms of specificity, reliability, and sensitivity. Future perspective: Future research should focus on expanding the use of imaging techniques and identifying new biomarkers that reflect early AD pathology [73–77].

9.4 Computed Tomography

CT is the oldest and most commonly used imaging method to evaluate patients with dementia. This technique has been used to determine reversible causes of dementia, such as normal pressure hydrocephalus, chronic subdural hematoma, mass injury (i.e., meningioma), and infection. Magnetic resonance imaging is preferred to identify specific pathologies such as medial temporal lobe atrophy, hippocampal formation, or parahippocampal gyrus, each of which is highly predictive of AD [9]. Magnetic resonance spectroscopy can be used for differential diagnosis and assessment of dementia progression.

Elevated inositol levels for creatine in the medial temporal lobe, increased levels of choline for creatine, decreased levels of N-acetylaspartate for creatine, and lower findings in the parietal lobe are markers of early AD [13].

Volumetric studies assess volume loss in the limbic system in structures such as the entorhinal cortex, hippocampus, amygdala, and hypothalamus. Magnetic resonance volumetric analysis can help in distinguishing patients with mild cognitive impairments (at risk of proceeding to AD) from normal elderly [14]. Several studies have shown cerebral perfusion in AD, other groups of dementia, and mild cognitive impairment patients.

Some studies have shown that decreased blood flow in the temporoparietal association area is common in the early stage of AD, before brain atrophy is detectable. As dementia progresses, blood flow decreases in the frontal lobe region and is relatively well preserved in the pons, primary motor cortex, and primary visual cortex of the occipital lobe, basal ganglia, and thalamus [11, 12, 15–32].

Synaptic activity in the brain depends on glucose metabolism, which is correlated with cerebral perfusion. These functions have been studied with 18F-fluorodeoxyglucose PET and SPECT using either technetium-99 m-hexamethylpropylene amine or technetium-99 m-ethyl cysteine diethyl ester oxime for early diagnosis of AD and differential diagnosis of other causes of dementia. The sensitivity and specificity of perfusion SPECT are quite adequate to distinguish AD patients from healthy individuals. When comparing the results generated by computed tomography of Alzheimer's disease (AD) and the use of 18F FDG (fluorodeoxyglucose) PET/CT, it can be seen that the latter is an excellent aid in the differential diagnosis of dementias, but that both methods have higher specificity than clinical criteria alone [9, 29].

In addition, the sensitivity and specificity of FDG PET for predicting progression to AD in MCI subjects were found to be 78–89% and 74–85%, respectively, compared to perfusion SPECT which was less specific but relatively equally sensitive [4, 30, 78].

However, in many previous studies, hypoperfusion and hypometabolism were estimated by visual qualitative analysis, which was subjective and depended on physicians' experience, while small reductions in perfusion and glucose metabolism were lost. Although more objective than visual analysis, the ROI method was rather biased by exploring exclusively the brain regions that should be involved, such as the parietal and temporal cortices, without taking into account other areas.

Furthermore, comparison of perfusion and metabolism between repeat studies of the same patient or between different patients was unreliable due to variations in brain position during acquisition as well as differences in size and shape [75–79].

9.5 Behavior Assessments

The diagnosis of AD, according to the standard criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA), is the mild to moderate DSM-III R [41], usually defined by Mini-Mental State Examination between 10 or 11 and 24 or 26.

The adverse effects of acetylcholinesterase inhibitors were, in general, well tolerated [35, 42–45]. Compared with placebo, cholinesterase inhibitors showed consistent effects in the domains of cognition and global assessment, but the summary estimate showed small effect sizes. Outcomes in the behavior and quality of life domains were less frequently assessed and indicated less consistent effects [46–49].

Most studies assessed cognitive outcomes with the 70-point ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive Subscale) and showed significant differences of 1.5 to 3.9 points in favor of cholinesterase inhibitors. Only 46% of randomized clinical trials discussed the clinical significance of their results, and most measures of clinical significance were based on opinion [49].

The review commissioned by the National Institute for Clinical Excellence (NICE) [50] regarding the effects of cholinesterase inhibitors on cognition and quality of life and adverse effects in patients with mild, moderate, and severe AD, with the aim of providing clinical criteria for England [49], concluded that the three inhibitors at higher doses showed benefit in the cognitive function, but the treatment effects were small, in the range of 3 to 4 points on the 70-point ADAS-Cog scale [39]. Behavioral and psychological symptoms of Alzheimer's disease are common throughout the disease and are a major cause of institutionalization, drug use, expensive care, and family burden. Several devices have been developed to systematically assess neuropsychiatric symptoms of AD. Most of these scales include symptoms assessed by informants, usually the patient's family and/or caregiver.

Description used:

- Neuropsychiatric symptoms and dementia or AD.
- Behavioral symptoms and dementia or AD.
- Neuropsychiatry and dementia or AD.
- Behavioral problems and dementia or AD.
- Behavioral and psychological symptoms of dementia (BPSD) and dementia or AD.

According to the surveys conducted , it can describe that the most widely used behavioral and psychological assessment scales in the world are BEHAVE-AD, CAMDEXR Part A (Cambridge Test for Learners), and Depression ScaleAlzheimer's disease (AD) behavior assessment and Dementia Mood Assessment Scale (DMAS) found in Assessment of Depressive Symptoms. The Cohen-Mansfield Agitation Inventory (CMAI) is widely used to assess a wide range of arousal symptoms.

The Cognitive Subscale of the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) was developed in the 1980s to assess the level of cognitive dysfunction in Alzheimer's disease, but as research progressed, it began to be used for pre-dementia populations. Therefore, the use of the ADAS-Cog has been extended to these pre-dementia studies; however, it should be noted that the ability to detect important changes in these milder pre-dementia stages of disease progression may be compromised. Therefore, if the ADAS-Cog cannot detect important changes, our understanding of pre-dementia disease progression may be compromised, and trials may incorrectly conclude that a new treatment approach was not

beneficial but as shown in several papers suggest that the original ADAS-Cog is not an ideal outcome measure for pre-dementia studies; however, given the prominence of the ADAS-Cog, care should be taken when considering the use of alternative outcome measures.

There are now more than 31 modified versions of the ADAS-Cog, and the modification approaches that seem most beneficial include changing the scoring methodology or adding tests for memory, executive function, and/or daily functioning. Although the modifications improve the performance of the ADAS-Cog, this comes at the cost of introducing heterogeneity that can limit the comparison between studies. Significant variation was found in the administration procedures and materials used for the ADAS-Cog-11 between clinical trials, which may weaken the reliability of the interobserver, intraobserver, and test-retest systems. Learning effects may also be a concern, as a statistically significant decline in ADAS-Cog-11 scores was found in individuals who otherwise did not appear to be progressing in symptoms, which should be a wake-up call for these studies [77, 79].

The Mini-Mental State Examination (MMSE) is designed to be a practical clinical assessment of cognitive status change in geriatric patients. It examines issues such as temporal and spatial orientation, short-term memory (immediate or attention), evocation, calculation, praxis, language, and visual-spatial skills. This test can be used as a screening tool for cognitive impairment or as a cognitive assessment.

The MMSE includes 11 items, divided into 2 sections. The first requires verbal responses to questions of orientation, memory, and attention, while the second assesses reading and writing and covers naming skills, followed by verbal and written commands such as writing a sentence and copying a drawing (polygons). All questions are completed in the order listed and can be scored immediately by adding up the points awarded for each successfully completed task. The maximum score is 30 [80].

Neuropsychiatric symptoms such as apathy, disinhibition, depression, psychosis, and agitation commonly accompany progressive cognitive and functional decline in Alzheimer's disease (AD), so many behavior and personality disorders are more variably manifested in AD than cognitive deficits, increasing recognition of symptoms, these being not only cognitive but also pathophysiological associated with the disease. On the other hand, neuropsychiatric symptoms can significantly contribute to the overall morbidity of AD in both patients and caregivers, emphasizing the importance of identifying and quantifying patient symptoms and their impact on caregivers. To facilitate these neuropsychiatric assessment processes we need to always seek a comprehensive and reliable, validated tool and that the symptom assessment scales are developed based on individual developmental, regional and other characteristics for a comprehensive clinical research study involving AD patients [77, 79, 81, 82].

The NPI was developed to indicate the severity and frequency of the main behavioral changes, typical of dementias such as apathy, euphoria, anxiety, agitation, depression, disinhibition, irritability, hallucinations, delusions, aberrant motor behavior, and sleep and appetite alterations. The score, from 0 to 144, is calculated

Table 9.2 Key differences in clinical tests for dementia assessment

Tests	Tracking system
IQCODE (informant questionnaire on cognitive decline in the elderly)	Report from a person who has lived with an elderly person for more than 10 years
Direct Assessment of Functional Status (DAFS)	Assesses seven different domains of functional abilities
DAD (disability assessment for dementia)	Quantify functional abilities and cognitive dimensions in the activity of daily living
Cambridge Cognition Examination (CAMCOG)	It assesses global cognitive function and impairments for the diagnosis of dementia
CERAD (consortium to establish a registry for Alzheimer's disease)	Relationship with sociodemographic variables and perceived health
MDRS (Mattis dementia rating scale)	Estimating the influence of low education and illiteracy on the assessment of dementias
Bayer scale	Activities of daily living and their efficiency in differentiating individuals with mild to moderate dementia from normal individuals
KATS scale	The ability of the elderly to take care of themselves and answer for themselves in the space of their own home
NPI (neuropsychiatric inventory)	An informant-based instrument that measures the presence and severity of 12 neuropsychiatric symptoms (NPS) in patients with dementia, as well as the distress Of the informant
MoCA (Montreal cognitive assessment)	Cognitive screening tool more sensitive than the mini-mental state examination (MMSE) to the milder stages of decline, namely, mild cognitive impairment (MCI)
MMES (mini-mental state examination)	Used to assess cognitive function because it is fast
CDT (clock drawing test)	"Screening test" for the start of an investigation into neurodegenerative disease

Source: Author himself

by multiplying the frequency by the intensity of symptoms (delusions, hallucinations, psychomotor agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nocturnal behaviors, and eating disorders). The higher the score, the greater the intensity and frequency.

The clock drawing test (CDT) and the verbal fluency (VF) test are simple to apply and widely used in neuropsychological assessments seeking to investigate dementia syndromes in the elderly. The diagnosis of Alzheimer's disease is clinical, but cognitive tests are of great help during the anamnesis. The objective of this work was to evaluate the correlation between verbal fluency and clock drawing tests and other cognitive instruments used to screen for Alzheimer's disease.

It consists of asking the elderly person to draw a clock face with numbers on it. It is considered a valid and reliable test for screening people with brain damage, because it checks the visual constructive ability or constructional praxis, presenting the ability to draw or build from a stimulus (in this case, a verbal command). It is

independent of verbal language, and for this reason, it is considered a non-verbal cognitive test. The task tends to be more complex and more abstract given its integrative nature with auditory input and motor output and greater need for memory use.

The Montreal Cognitive Assessment (MoCA) is a brief cognitive screening instrument, presenting a quick, practical, and effective method for distinguishing the performance of adults with normal cognitive aging from adults with cognitive impairment. It basically consists of a one-page protocol, with an application time of approximately 10 minutes, and a manual where the instructions for administering the tests are explained and the system for rating performance on the items is defined. With a maximum score of 30 (points), the MoCA evaluates eight cognitive domains, contemplating several tasks in each domain, according to the structure described in Table 9.2 [23, 83–86].

As we can see, there is a range of tests and applications that aim to facilitate the analysis of initial symptoms, but we certainly need researchers and analyzers prepared globally to identify the signs of Alzheimer's disease; we saw that the pathological processes, the triggering of disease, the biomarkers that have been demonstrated, and the imaging equipment, this whole arsenal, need a human component and training focused on the quality of life of the human being. Our resources are still widespread in the installed disease, and with this, we lose the macrovision of human life since childhood, that is, we take good care of pathologies and diseases, but we still lack a clear understanding of the cellular control mechanisms in the most comprehensive way possible for the development of the human being, and it is up to us to know his genetics and all epigenetic elements, the action of nature and healthy food from his birth to his death, not so that we can achieve immortality, but to improve the quality of life of people in the future, thinking about their present.

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Chapter 10
New Perspectives for Treatment in Alzheimer's Disease

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10.1 Introduction

The amyloid cascade hypothesis, a widely accepted model formally proposed in 1992 [50], is characterized by the sequence of deposition of Aβ peptide in neuritic plaques, followed by the induction of neurotoxic events that form NFT, resulting in cell loss and vascular damage [15]. The amyloid pathway, a very early event in the disease, starts in the hippocampus and entorhinal cortex [50, 71, 90, 96, 100]. The recent failure of anti-amyloid therapies has been questioning this temporal sequence. Evidence suggests that biomarker development in preclinical or prodromal AD does not follow the timeline proposed by the amyloid cascade hypothesis [62]. A significant number of high-profile phase III clinical trials recently failed while exploring the amyloid cascade hypothesis. Some studies have reported that up to 25% of individuals clinically diagnosed with mild-to-moderate AD show sparse neuritic amyloid plaques on postmortem examination [75, 105, 115]. These findings raise questions on the use of this single target in some clinical trials, maybe explaining their recent failures as disease modification in AD requires accurate diagnosis at the

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pre-dementia and preclinical stages [6, 29]. Uniform criteria to guide therapeutic trials are of utmost importance, as the clinical diagnosis may not be accompanied by the expected neuropathological changes, resulting in failure of interventions. The development of the A/T/N research framework represented a significant step forward, since AD stages with their different neuropathological alterations would diminish the risk of overlap [57].

Pharmacotherapies for the treatment of Alzheimer's disease (AD) can be divided into two categories: symptomatic and disease-modifying therapies (DMTs). Cholinesterase inhibitors (*rivastigmine*, *galantamine*, and *donepezil*) and the N-methyl-D-aspartate receptor antagonist (*memantine*) are the only drugs approved for the treatment of cognitive symptoms in AD and are considered symptomatics in the treatment of the disease. During the last decade, studies have identified molecular targets for specific AD therapies, with focus in earlier interventions. These targets include the senile or neuritic plaques and fibrillary β-amyloid (Aβ) or Aβ oligomers at the pre-dementia stage, preventing Aβ accumulation. β-amyloid peptides spontaneously aggregate, triggering oxidative injury, microglial and astrocytic activity, as well as abnormal kinase/phosphatase activity. In a not completely understood manner, Aβ also induces the spread of tau pathology, which is associated with necroptosis (neuronal death). Overproduction of Aβ, abnormal β-amyloid precursor protein (APP) metabolism, and reduced Aβ clearance are the mechanisms that the therapies would prevent from happening. In fact, preventing Aβ accumulation was the mechanism of most drugs tested for AD in the past 20 years [90]. On the other hand, in cytoskeletal degeneration, i.e., tau pathology, neurofibrillary tangles (NFTs) would be the primary target. All these mechanisms are focused in the amyloid cascade hypothesis and tau biology. However, in earlier stages, upstream alterations causing NFT formation could be considered better targets [59, 109].

There is an uncertainty on which, amyloid or tau, would be the best target. However, therapies targeting both amyloid and tau would represent a promising alternative. Other mechanisms studied in recent clinical trials that lead to secondary toxicity are inflammation, oxidative stress, glial activation with molecular targets being β-secretase (BACE), tau protein, markers of inflammation, and even the 5-HT2A receptor [25, 36, 38, 80, 129].

As mentioned above, drug development for AD has consistently shown a high failure rate in recent years [36]. From 413 AD trials testing 244 drugs carried out between 2002 and 2012, almost all failed in their respective clinical trials, with the exception of the memantine trial in the early 2000s [23]. Although, in the beginning of 2020, 29 agents were being studied, there are still no new DMTs available for AD [26]. For most of these trials, although preliminary results were promising, like drug-target engagement, with reported Aβ clearance from the brain [36, 79], they failed to demonstrate cognitive or clinical improvement occurring together with the observed changes in neuropathological parameters [25].

In this chapter, we aim to gather the available new perspectives on treatment of Alzheimer's disease, including compounds and their respective clinical trials with different mechanisms of action like oxidative stress and inflammation, vaccines and immunotherapies, and enzyme inhibitors, with a final discussion on other perspectives.

10.2 Oxidative Stress

10.2.1 Oxidative Stress

The presence of oxidative stress in neurodegenerative diseases such as AD is somehow well established. There is a link between oxidative stress and AD etiology. In fact, studies suggest that oxidative stress occurs earlier in the process of AD pathology, with markers of oxidative stress found in mild cognitive impairment [8]. When interacting with the Aβ, metal ions with redox properties can catalyze the production of reactive oxygen species (ROS), contributing to oxidative damage on the Aβ peptide itself and on other surrounding molecules. These metal ions, i.e., zinc, iron, and copper, act as modulators of the amyloid cascade and play a role in Aβ aggregation [34, 127]. Either overproduction or insufficient elimination of ROS leads to their accumulation and defines oxidative stress. Another identified pathway of AD pathogenesis by oxidative stress is mitochondrial dysfunction by ROS generation, resulting in the overproduction and less clearance of free radicals secondary to deficiencies of the enzymes of the Krebs cycle [44, 113, 141].

Two mechanisms synthesize oxidative stress in the context of AD: the oxidation of neuronal membrane biomolecules like lipids, proteins, and nucleic acids, with membrane integrity disruption, and the oxidation of a protein responsible for Aβ clearance, the low-density lipoprotein receptor-related protein 1 (LRP1). Macrophages also play a key role, constituting a significant source of ROS [46]. Recent research is dedicated to understanding the oxidative damage of the Aβ and its relation to metal ions and ROS production, targeting specific therapies. Endogenous or exogenous molecules called antioxidant compounds, when in regulated concentrations, are capable of delay or inhibit oxidative stress by different processes. The oxidative damages seen in brains of people diagnosed with AD are frequently attributable to oxidative stress. However, the timeline of the occurrence of these known changes is yet to be fully understood with impact in the use of these changes as therapeutic targets [21].

Although present in a less quantity, the redox-competent copper (Cu) ions have higher toxicity of the ions involved and are considered the main therapeutic target. Zinc (Zn) is also considered a therapeutic target in recent studies. The strategies involving these ions are chelators that would remove these metals ions and their Aβ-bound species to achieve detoxification. Only a few small molecules are now in study. They are able to interact with copper aiming at reversing the cognitive deficit. The following studies are ongoing and use animal models [22].

The update on drug development published annually by Cummings et al. [26] reports an annual update on clinical trials with the purpose of disease modification, cognitive enhancement, and control of NPS. As of February 2020, there were 97 agents with the objective of achieving disease modification. Of these, 29 agents were in 36 phase III clinical trials. At the beginning of 2019, three clinical trials in phase III were biological therapies investigating symptomatic cognitive enhancers and disease-modifying small molecules directed at oxidative stress and inflammation. In 2020, five clinical trials in phase III were biological therapies with these

objectives. Table 10.1 summarizes these trials. We included only biological therapies in phase II and III trials with pathways of interest for this section. Multiple mechanisms, events, and insults exist that are capable of increasing oxidative stress and cause neuronal dysfunction like aging, ischemia, and inflammation. Therefore,

Table 10.1 Agents in phase II/III of Alzheimer's disease drug development targeting oxidative stress and inflammation

Agent	CADRO mechanism class	MOA Therapy type	FDA status Therapeutic purpose
ALZT-OP1 Cromolyn sodium, Intal, ibuprofen	Inflammation	Mast cell stabilizer (cromolyn), anti-inflammatory (ibuprofen)	Alzheimer's disease (phase III) Microglial modulation; promote microglial clearance of amyloid (DMT)
CHF 5074	Amyloid-related inflammation Others	Small molecule	Mild cognitive impairment (phase II)
COR388	Inflammation Infection	Bacterial protease inhibitor targeting gingipain produced by *P. gingivalis*	Reduce neuroinflammation and hippocampal degeneration (DMT)
Deferiprone Ferriprox	Metals	Small molecule	Alzheimer's disease (phase II)
Epigallocatechin gallate (EGCG) Sunphenon EGCg	Amyloid-related inflammation Others	Dietary supplement	Alzheimer's disease (phase II/III)
GV-971 Sodium oligomannate, sodium oligomannurarate	Amyloid-related inflammation	Small molecule	Alzheimer's disease (phase III)
Icosapent ethyl (IPE)	Synaptic plasticity Neuroprotection	Purified form of the omega-3 fatty acid EPA	Improve synaptic function; reduce inflammation (DMT)
Montelukast Singulair, MK0476	Inflammation	Small molecule	Alzheimer's disease (phase II)
Neflamapimod VX-745	Inflammation	Small molecule	Alzheimer's disease (phase II)
PBT2	Amyloid-related metals	Small molecule	Alzheimer's disease (phase II)
Pioglitazone AD4833, Actos®, Glustin™, Piozone®	Inflammation, others	Small molecule	Mild cognitive impairment (phase III)
Thalidomide Thalomid®	Amyloid-related inflammation	Small molecule	Alzheimer's disease (phase II/III)
Varoglutamstat PQ912	Amyloid-related inflammation	Small molecule	Alzheimer's disease (phase II)

CADRO Common Alzheimer's Disease and Related Disorders Research Ontology, *MOA* mechanism of action; Phase II/III trials (Adapted from [26])

we also included in Table 10.1 compounds that aim to treat inflammation in patients eligible to clinical trials of AD treatment.

Other mechanisms of action have been studied, most of them still using animal models and some already using humans. These include chelators, metamorphosizers, and receptors for advanced glycation end products (RAGE). They still show mixed results. Studies have been reporting that donepezil and rivastigmine have antioxidant properties. The mechanisms of action are a stimulating effect in the activity of the enzyme catalase and in the glutathione concentration in macrophages [46].

10.2.2 Chelators

10.2.2.1 Clioquinol (5-Chloro-7-Iodo-Quinolin-8-Ol) and PBT2 (a 8-Hydroxyquinoline Analog)

This chelator is known to inhibit Aβ accumulation, and its derivative, 2-(dimethylamino)methyl-5,7-dichloro-8-hydroxyquinoline (PBT2), a copper/zinc ionophore with a more blood-brain barrier permeability, would improve cognition in AD model mice [3]. PBT2 was the subject of three phase II clinical trials for Alzheimer's disease (EURO, IMAGINE, and IMAGINE EXTENSION), resulting in mixed but promising results. Continuation of the studies with higher doses was proposed [68, 134].

10.2.2.2 Bis-8-Aminoquinoline Derivatives (PA1637)

These copper-specific chelating agents or ligands have a three to four times affinity for copper when compared to 8-hydroxyquinoline monomers like clioquinol. They have the properties of Aβ peptide solubilization and H_2O_2 produced by Cu-amyloids activated by ascorbic acid inhibition [78].

10.2.3 Metamorphosizers

Metamorphosizers are chemical tools developed with the objective of targeting metal-Aβ complexes. They would alter the interaction between metal ions and Aβ, redirecting the toxic aggregation pathway to a less toxic unstructured Aβ form and reducing ROS production, which eventually alleviates metal-Aβ-linked toxicity. The chemical tool called L2-b, that modulates metal-induced Aβ aggregation, is reported to be able to attain these objectives with relative metabolic stability [103, 108].

10.2.4 Receptors for Advanced Glycation End Products (RAGE)

The blood-brain barrier (BBB) can be compromised due to endothelial cell damage and dysfunction. As a result, Aβ transport may be impaired because of two mechanisms: the dysfunctional transportation itself by the receptor for advanced glycation end products (RAGE) and binding of Aβ to neurons which enhances formation of toxic ROS. RAGE inhibition would address neuroinflammation and oxidative stress. A phase III study, STEADFAST, of Azeliragon (11, TTP488, vTv Therapeutics, NCT03980730), an oral, small-molecule inhibitor of RAGE, was terminated in mid-2018 after failing to meet its co-primary endpoint [16, 36, 63]. Two extensions were proposed but were terminated by the end of 2020 for the same reason (results not yet published).

10.3 Active and Passive Immunotherapy

Although amyloid deposits are known as one of the hallmarks in the amyloidogenic pathway, recent findings suggest that Aβ oligomers (a neurotoxic soluble form of Aβ) are especially important as an early trigger of AD pathology, presenting a closer relation to AD symptom progression than the deposit of plaques [11]. In preclinical models and brains of patients with AD, Aβ oligomers (from dimers to dodecamers and pyroglutamate forms) are implicated in synapse damage and tau hyperphosphorylation and neuroinflammation [126].

In animal models of DA (PDAPP – transgenic mice which overexpressed human mutant APP), Schenk et al. first found that immunization of young animals with an anti-amyloid compound prevented AD-like neuropathologies, i.e., the development of Aβ plaques, neuritic dystrophy, and astrogliosis. This effect was also observed in older animals, in which immunization reduced the extent and progression of these neuropathological hallmarks of AD [110]. Since then, a number of anti-amyloid compounds, encompassing active and passive immunotherapies, have been developed and tested in clinical trials, with the objective of removing the Aβ peptide from the brain parenchyma and/or reducing its aggregation. Aβ peptides are produced from sequential cleavage of the APP, including $A\beta_{40}$ and $A\beta_{42}$. $A\beta_{40}$ is the most abundant variant (90%) among the secreted Aβ forms and can produce highly toxic diffusible aggregates [50, 117, 131]. However, $A\beta_{42}$ is more hydrophobic, more prone to aggregate, and $A\beta_{42}$ oligomers are regarded to be the most neurotoxic species [124, 133]. Hence, the principle behind passive immunotherapy for AD is to lessen Aβ burden in the brain with the use of anti-amyloid compounds, a series of monoclonal antibodies (mAb) against different portions and forms of the Aβ peptide.

Nevertheless, most passive immunotherapy agents, despite successfully removing amyloid deposits from the brain parenchyma, failed to show significant cognitive and functional improvement in patients with AD. These findings suggest that

therapeutic interventions targeting the Aβ peptide should be implemented years before the occurrence of amyloid deposition. In fact, compounds that engage soluble forms of Aβ oligomers appear to be more effective when compared to agents targeting insoluble amyloid plaques and fibrils [130]. Ongoing clinical trials are focused on earlier stages of AD and asymptomatic at-risk subjects.

An important limitation concerning the use of mAb against Aβ is the concomitant removal of vascular amyloid when targeting the neurotoxic Aβ peptides, resulting in vasogenic edema and/or microhemorrhages evidenced as hyperintensities on MRI sequences such as FLAIR (reflecting parenchymal edema or sulcal effusion) or T2-weighted gradient echo (indicating iron deposits in the form of hemosiderin) [93, 121]. These abnormalities are known as ARIA (amyloid-related imaging abnormalities), and they can be divided into different subtypes: ARIA-E when effusions are present and ARIA-H reflecting microhemorrhages [20, 121].

Aside from anti-amyloid antibodies, the quest for developing disease-modifying immunotherapeutic strategies for AD also includes research for active immunotherapeutic agents. Vaccines are largely recognized as one of the most cost-effective and yet impactful medical therapeutic initiatives. *AN1792* was the first active Aβ immunotherapeutic compound to be tested in a phase II CT that demonstrated induced immune response in AD patients [45]. The drug had to be discontinued after the detection of meningoencephalitis as an adverse event in a subset of subjects [85]. Subsequent immunotherapeutic attempts have explored alternate mechanisms aiming for better safety profiles. Nevertheless, the main advantage in the designing of vaccines remains the possibility to induce the patient's own immune system to produce antibodies, therefore avoiding problems such as the anti-drug human antibodies that haunt mAb therapeutics [95].

The following sections will discuss the main compounds that target AD neuropathological components, including active and passive immunotherapies.

10.3.1 Vaccines

10.3.1.1 ABvac40

ABvac40 is an investigational vaccine targeting the C-terminus of $A\beta_{40}$. The rationale for its development relies on the fact that several studies distinguish the high concentration of $A\beta_{40}$ peptide in the brain as an indication of cognitive deterioration both in AD and in Down syndrome [76, 94, 136].

A phase I, double-blind, randomized, placebo-controlled clinical trial (DBRCT) enrolled a small number of individuals ($n = 16$ for the active groups and $n = 8$ for placebo) and aimed to assess the safety and tolerability of *ABvac40* in mild-to-moderate AD patients [67]. Throughout the study, subjects underwent a full safety control assessment that included telephone interviews, hospital visits, and clinical examination up to 1 year after the last subcutaneous infusion in order to investigate potential neurologic, psychiatric, and/or cardiovascular adverse events. There were

no significant differences in the incidence of adverse effects between groups. No occurrence of ARIA-E or ARIA-H was observed with *ABvac40* during the study.

There is an ongoing phase II (NCT03461276), multicenter DBRCT that recruited subjects with amnestic MCI or very mild AD to investigate the safety, tolerability, and immune response of repeated subcutaneous injections of *ABvac40* at 4-week intervals yielding a total of six doses. The start date was February 2018 and the estimated end date is December 2022.

10.3.1.2 GV1001

Originally developed as a cancer vaccine, *GV1001* is a 16-amino acid peptide comprising a sequence from the human enzyme telomerase reverse transcriptase (hTERT), which is recognized to have a strong antioxidant activity. Most types of cancer highly express hTERT, and immunization with GV1001 intends to activate the immune system, specifically T cells, to recognize and remove tumors [53, 72]. *GV1001* has been shown to have various biological functions in non-cancer cells, such as an anti-inflammatory effect and neuroprotective outcomes by inhibiting neurotoxicity, apoptosis, and the production of reactive oxygen species induced by Aβ in neural stem cells [65, 91]. Studies attribute these actions to *GV1001*'s ability to reproduce hTERT's extra-telomeric antioxidant, anti-apoptotic, and pro-survival functions [91, 92].

In conformity with this rationale, in 2017, *GemVax & KAEL* began a phase II trial to assess safety and efficacy of *GV1001* in people with mild-to-moderate AD in Korea. The study enrolled 90 AD patients, who were randomized to receive 4 weekly subcutaneous injections of 0.56 mg or 1.12 mg of *GV1001* or placebo, followed by biweekly injections for 24 weeks, making for a total of 14 injections. The primary outcome at 24 weeks was change on the Severe Impairment Battery (SIB); and secondary outcomes included measures of cognition and functionality, i.e., the Korean Mini-Mental State Examination (MMSE), the Clinical Dementia Rating Sum of Boxes (CDR-SoB), the Neuropsychiatric Inventory (NPI), the Global Deterioration Scale (GDS), the ADCS-Activities of Daily Living (ADCS-ADL), and the Clinician Interview-Based Impression of Change (CIBIC). The company presented their results at the 12th Clinical Trials on Alzheimer's Disease (CTAD) 2019 International Conference. The study met its primary endpoint, with vaccinated participants stabilizing on the SIB (0.12 point drop), whereas those on placebo dropped by 7.23 points. Dose-response was not shown, and adverse events were similar across all three groups. In November 2020, the company released new data on this phase II trial showing a statistically significant improvement in the NPI and, though statistically not significant, an improvement trend in functionality scale ADCS-ADL. They also announced that based on these results, the company was planning to submit a phase III application.

A second phase II trial is registered (NCT03959553) to be conducted in the United States. It has the same number of participants (n = 90), inclusion criteria, and

dosing plan as the Korean trial. The primary outcome will be the number of patients who improve on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); and secondary outcomes are 24-week changes in similar measures of cognition and function as the prior study.

10.3.1.3 AADvac1

Tau protein is a vital component of the cytoskeleton and a multifunctional molecule that takes an essential part in various cytosolic activities such as microtubule stabilization and integrity, maintaining neuronal cell shape, axonal transport, and synapse formation [48]. Under stress conditions, tau has been shown to translocate into the nucleus to protect DNA from fragmentation [123]. Modifications of tau protein, such as phosphorylation and truncation, have been linked to many neurodegenerative diseases such as AD, corticobasal degeneration, progressive supranuclear palsy (PSP), and frontotemporal dementia. *AADvac1* (axon peptide 108 conjugated to KLH) is an active vaccine designed to generate an immune response against pathologically modified forms of tau protein [89]. The first phase I clinical study of *AADvac1* (NCT01850238) enrolled 30 participants, paired with placebo, for 24 weeks. The vaccine demonstrated a favorable safety profile, with adverse events resuming to mild injection site reactions. Outcome measures of cognition were not statistically significant [80].

A second phase I (NCT02031198), 72-week, open-label, follow-up CT, entitled FUNDAMANT [81], was conducted with mild-to-moderate AD patients who had completed the first phase I study. Primary objective involved safety assessments, and secondary outcome measures investigated antibodies' immunogenicity and their capacity to bind to AD tau. Safety profile was beneficial as the main adverse effects were injection site reactions. *AADvac1* induced production of immunoglobulin G (IgG) against the tau peptide which remained for approximately 6 months and gradually declined, requiring booster doses for restorage. There was a tendency toward less hippocampal atrophy and slower rates of cognitive decline in subjects with higher IgG titers.

A phase II DBRCT (NCT02579252) called ADAMANT was initiated in 2015 and recruited individuals with mild AD paired with placebo. Subjects received 6 doses of *AADvac1* in 4-week intervals and then 5 doses in 3-month intervals, for a total of 11 doses over a period of 2 years. The primary outcome was safety; secondary outcomes included cognitive and clinical batteries as well as measure of immunogenicity. The trial was completed in mid-2019. In a September 2019 press release [9], Axon Neuroscience announced initial results and provided more details at the 2020 virtual AAT-AD/PD Focus Meeting [1]. According to their reports, there were no differences in incidence or type of adverse event between treatment and placebo groups. More than 80% of immunized participants developed high-affinity tau antibodies. Moreover, the report announced *AADvac-1* slowed the increase in plasma neurofilament light (NfL), a recognized neurodegeneration biomarker; promoted

reduction of CSF pTau181 and pTau217 and stabilization of total tau compared with placebo; and led to statistically significant slowing of cortical atrophy and significant white matter integrity preservation with treatment compared with control. However, treatment produced no cognitive benefit, and a second analysis indicated a trend toward slower decline with treatment than placebo on the CDR-SoB, MMSE, and ADL among younger participants, though not statistically significant.

10.3.2 Amyloid-Based Passive Immunotherapy

10.3.2.1 Bapineuzumab (AAB-001)

Bapineuzumab, the first monoclonal antibody (mAb) to be tested in humans, is a humanized immunoglobulin (IgG1) that targets aggregated fibrillary amyloid and soluble peripheral Aβ by binding to the N-terminus of the Aβ peptide [59, 73]. Antibody binding to deposited Aβ triggers microglial activation. The microglia cells then clear the deposited plaques through Fc receptor-mediated phagocytosis and subsequent peptide degradation [10].

The drug was initially tested in four phase III trials which enrolled patients with mild-to-moderate Alzheimer's disease. Since phase II trials, also with mild-to-moderate AD, showed a reduction in p-tau levels in CSF and lowering of the average uptake of PiB in PET scan attributed to *bapineuzumab* exposure [12, 101], the phase III trials were designed in a way that separated ApoEε4 allele carriers and noncarriers. *Bapineuzumab* dose was limited in carriers to minimize the risk of ARIA-E [104].

In the first two phase III studies (301 and 302), during over 18 months of treatment, no clinically relevant benefits were evidenced in patients with mild-to-moderate Alzheimer's disease among APOEε4 carriers and noncarriers [105]. The occurrence of ARIA-E was an important adverse event related to *bapineuzumab* use, particularly at higher doses and among APOEε4 carriers (46% vs 58%) [69]. The other two of these practically identical phase III trials (3000 and 3001), despite including a more global demographic, also found no differences regarding the cognition and functionality endpoints [132].

Later, to address the long-term safety and tolerability concerns of *bapineuzumab* treatment, two follow-up phase III extension studies were conducted (3002 and 3003), in which subjects from the previous parent RCTs (3000 and 3001) were recruited to receive *bapineuzumab* regardless of previous enrollment in the placebo or treatment group. The objective was to assess the rate of adverse events, mainly ARIA-E [56]. The incidence of ARIA-E was higher among those who received the antibody for the first time (11.8% in APOEε4 carriers vs 5.4% in noncarriers) when compared to subjects who had already received the compound in the previous studies (5.1% and 1.3%, respectively). These findings suggest a reduction in the risk for ARIA-E over time if treatment is continued [106, 107].

10.3.2.2 Solanezumab (LY2062430)

Solanezumab is a humanized IgG1 mAb that recognizes the mid-domain of soluble monomeric Aβ peptide, known to be present in Alzheimer's disease senile plaques. Different from *bapineuzumab*, the rationale of *solanezumab* mechanism of action is to increase the clearance of soluble monomeric Aβ, thus modifying the balance between peripheral and central nervous system amyloid peptide concentrations, which results in decreasing Aβ deposition [118].

In two phase III DBRCT (EXPEDITION and EXPEDITION2), subjects with mild-to-moderate Alzheimer's disease were assigned to receive either *solanezumab* or placebo. After 80 weeks of treatment, no improvements in cognition or functional abilities were found [28]. Nevertheless, a planned secondary analysis suggested that the use of *solanezumab* in the subgroup of patients with mild Alzheimer's disease, during a period of 18 months, may be associated with slower rates of cognitive and functional decline when compared to placebo [119].

In regard to safety, data analysis with the combined samples of both trials found a low incidence of ARIA-E in *solanezumab*-treated patients (1.1%), ratings statistically similar to the placebo group (0.55%). The ARIA-H events in the *solanezumab* group were also not statistically different from the placebo group (9.1% vs 7.3%). An interesting finding is that ARIA-E and ARIA-H co-occurred in 71% of the patients, afflicting the same brain regions in 48% of the cases [119]. The low incidence of ARIA-E is probably explained due to the fact that the drug targets soluble Aβ, but not fibrillary amyloid plaques, thus resulting in a small incidence of edema and hemorrhage [28, 98].

The positive findings related to the mild AD subgroup analysis (EXPEDITION2) and the low incidence of ARIA-E in both previous studies encouraged a third RCT in patients with mild AD (EXPEDITION3). In this phase III DBRCT, inclusion criteria were scores of 20–26 in the MMSE and evidence of Aβ pathology (i.e., positive florbetapir PET or lower concentrations of CSF $A\beta_{42}$). It is interesting to notice that patients continued with their standard treatment for AD (cholinesterase inhibitors and/or memantine) along the RCT. The trial lasted 76 weeks, with participants receiving intravenous infusions *solanezumab* or placebo every 4 weeks.

The effects of *solanezumab* exposure were assessed through global cognition (at baseline and week 80) and structural neuroimaging (MRI). Although the results failed to show reduction on global and specific brain regions' atrophy [112], like in the previous studies, no statistically significant differences between groups regarding adverse effects were found [52].

10.3.2.3 Gantenerumab (RO4909832)

Gantenerumab is the first fully humanized IgG1 mAb, designed to bind to aggregated Aβ, with affinity to N-terminal ($A\beta_{3–12}$) and middle portion ($A\beta_{18–27}$) domains of the Aβ peptide [82]. Aggregated Aβ (plaques) are removed through FC receptor-mediated microglial phagocytosis [87].

In a phase III RCT (SCarlet RoAD study, SR), patients with prodromal AD who received *gantenerumab* showed no benefits over the placebo group concerning the primary and secondary endpoints of the study (global cognitive and functional state and amyloid-related biomarkers, respectively). The study was discontinued for futility after 50% of the subjects completed 2 years of follow-up. Nevertheless, some dose-dependent effects were detected in exploratory analyses on select clinical and biomarker endpoints (reduction in amyloid load on PET and CSF p-tau, t-tau, and neurogranin), suggesting that higher doses of *gantenerumab* could have treatment potential. Unfortunately, there was also a dose-dependent increase in the incidence of ARIA, particularly in APOEε4 carriers: ARIA-E occurred in up to 15% of patients and ARIA-H in 32%. Most patients with ARIA were asymptomatic, and safety parameters were later reassessed, but even a gradual dosage escalation was not able to prevent these MRI abnormalities [88].

Gantenerumab effects were also assessed in phase III RCT with mild AD patients (Marguerite RoAD study, MR). After the interruption of the SR study for futility, MR was converted to an open-label extension (OLE) that also found reduction in AD biomarkers in CSF [135]. Since the low-dose trials were considered safe, the patients from MR are now enrolled in two ongoing OLE phase III trials, GRADUATE 1 and 2, to assess the impact of *gantenerumab* with longer exposure and higher doses. No new or unexpected findings concerning safety and efficacy were found [2, 5].

10.3.2.4 Crenezumab (MABT5102A)

Crenezumab is a fully humanized anti-Aβ IgG4 mAb that targets mid-domains of $A\beta_{40}$ and $A\beta_{42}$ in oligomeric and aggregated fibrillary forms [4]. The antibody was designed to have a reduced effector function, with lower Fcγ receptor-mediated inflammatory activation of the microglia, but maintaining microglial phagocytosis and removal of Aβ oligomers. The result is a lower risk of inducing ARIA-E and ARIA-H [138].

The efficacy and safety of the drug were assessed in two phase II trials that enrolled patients with mild-to-moderate AD. In the first study (ABBY), neither primary efficacy (cognition improvement) nor secondary outcome measures (functional status) were met [24]. The BLAZE study, another phase II DBRCT, also found no statistically significant results over placebo concerning cognitive and functional improvement [107]. In both of these trials, the incidences of microbleeds and cortical siderosis (ARIA) were lower than the ones found in trials with other anti-Aβ mAb compounds.

Although the phase II trials showed negative results concerning its primary endpoints, exploratory post hoc analyses suggested that the use of higher doses of *crenezumab* could be beneficial as an early intervention in the subgroup of mild AD patients. Hence, two phase III studies with prodromal-to-mild AD patients (CREAD and CREAD2) explored the efficacy and safety of *crenezumab* at a dose four times

higher than the ones used in the previous phase II trials (60 mg/kg vs 15 mg/kg) [90]. Safety profile was similar to what was observed in previous trials. Based on pre-planned interim analysis, both of these studies were discontinued [35].

10.3.2.5 Aducanumab (BIIB037)

Aducanumab is a fully human IgG1 mAb that targets the N-terminal and mid-domain of Aβ aggregates, comprising soluble oligomers and insoluble fibrils [7]. This recombinant antibody was isolated from blood lymphocytes (B cell) of cognitively healthy elderly subjects and has low affinity for monomeric Aβ. Activation of the microglia mediated by Fcγ receptor with subsequent phagocytosis appears to play an important role in Aβ clearance. Since the mAb was designed to bind preferentially to parenchyma Aβ over vascular Aβ, thus resulting in less microbleeding or vasogenic edema (ARIA), it was possible to use higher doses of aducanumab in clinical trials [116].

In the phase Ib PRIME trial with Aβ-PET-positive AD patients, *aducanumab* treatment resulted in a dose-dependent and time-dependent clearance of Aβ plaque load after 1 year of monthly injections, as evidenced by amyloid PET imaging. Subjects also showed slowing of cognitive decline measured by CDR-SoB and MMSE scales. However, 22% of the subjects who received *aducanumab* developed dose-dependent ARIA-E, especially the APOEε4 group. Still, *aducanumab* was the first compound to show a decrease in Aβ load in the brain and positive effects on cognition and global clinical status [116].

Later, two phase III RCTs – ENGAGE and EMERGE – enrolled individuals with mild cognitive impairment and mild dementia due to AD, confirmed by amyloid PET imaging. Both trials used the CDR-SoB as their primary endpoint [111]. The studies showed a clear dose-dependent reduction in brain Aβ levels associated with *aducanumab* treatment (identified through PET imaging), but the findings concerning the rate of cognitive decline were discrepant. While EMERGE showed a positive trend with high doses of *aducanumab*, no benefits with low or high doses were seen in ENGAGE. Since the prespecified outcome required positive results in both trials, the studies were interrupted for futility analysis [114]. Nevertheless, a post hoc analysis of the data claimed that *aducanumab* was efficacious on both halted trials, and the drug was submitted for FDA approval [64]. Once the statistical review of the FDA was negative, the Advisory Committee voted against approval of the drug, but the FDA Office of Neurological Drugs was more positive [66] .

10.3.2.6 Donanemab (LY3002813)

Donanemab is a humanized IgG1 antibody directed at an N-terminal pyroglutamate Aβ epitope that is present only in established plaques. It is specific for this epitope and shows no off-target binding to other Aβ species, neurotransmitters, or their

receptors and has no known symptomatic effect [55]. It was designed to clear Aβ plaques through microglial activation. In animal models, the mAb removed amyloid plaques with no microhemorrhage increase [27]. In phase I studies involving patients with amyloid-positive mild cognitive impairment or mild-to-moderate AD with dementia, *donanemab* reduced the amyloid plaque level even after a single dose, as measured by amyloid PET imaging [37].

A phase II trial was later conducted with early symptomatic Alzheimer's disease patients who had tau and amyloid deposition on PET imaging (TRAILBLAZER-ALZ study). The primary outcome was to assess disease progression through the score on the Integrated Alzheimer's Disease Rating Scale (iADRS). Secondary outcomes evaluated changes in clinical status (the CDR-SoB, the ADAS-Cog13, the ADCS-iADL, and the MMSE) and biological biomarkers (amyloid and tau burden, assessed by PET imaging, and possible changes on volumetric MRI). The trial found a modest positive impact of *donanemab* use on the primary outcome, i.e., improvement on cognition and functionality as indicated by change from baseline in the iADRS. The results for most secondary outcomes showed no substantial difference. The incidence of ARIA-E was significantly higher in the *donanemab* group than in the placebo group (26.7% vs 0.8%). Symptomatic ARIA-E was reported by 6.1% of all participants in the *donanemab* group (22% of those with ARIA-E) [74].

10.4 Enzyme Inhibitors

Although in clinical practice rivastigmine is primarily prescribed to ameliorate symptoms of dementia, some evidence suggests the drug can have a disease-modifying activity. By increasing the level of several α-secretases, thus redirecting the APP processing toward the non-amyloidogenic pathway (reduction of the generation of Aβ peptide), rivastigmine may have neurotrophic and neuroprotective actions (1,2). The drug also increases acetylcholine, and the agonist action in nicotinic and muscarinic receptors also increases α-secretase activity with consequent reduction in Aβ production (2,3).

10.4.1 BACE Inhibitors

Beta-secretase, also known as *b-site APP-cleaving enzyme 1* (BACE1), is involved in the defective cleavage of APP that leads to the production of the toxic Aβ peptide, a protagonist in the amyloid cascade hypothesis of AD [71, 139]. With the rationale of decreasing Aβ burden in the brain, the same that led to the development of a number of passive immunotherapeutic agents that target different forms of the Aβ peptide, research also explored the possible benefits of BACE inhibition. Hypothetically the decrease in Aβ production would result in slowing the

progression of AD, but clinical trials failed to show such results, increasing the skepticism toward some of the possible targets suggested by the amyloidogenic pathway [30, 90, 129].

In regard to side effects, rise of liver enzymes, skin rash, hair depigmentation, and ocular (retinal) abnormalities are a result of off-target binding, including inhibition of BACE2 and cathepsin D (CatD) [19, 60, 142]. Compounds designed to selectively target BACE1 try to avoid such complications of treatment [77].

10.4.1.1 Atabecestat (JNJ-54861911)

Atabecestat is a compound developed to treat AD through BACE inhibition and consequent reduction of Aβ production. In healthy human subjects (elderly and young), the drug achieved significant and sustained reduction of Aβ in CSF and plasma (up to 95% in both cases), confirming target engagement with BACE1 [128]. In a phase I study with asymptomatic AD patients presenting high levels of brain amyloid, *atabecestat* treatment resulted in a dose-dependent reduction of $A\beta_{40}$ (70–90%) and also of other Aβ fragments ($A\beta_{37}$, $A\beta_{38}$, and $A\beta_{42}$) in the CSF and plasma. There was also a decrease in sAPPβ and increase in sAPPα levels in CSF [129].

In phase II/III RCT enrolling participants with preclinical AD (EARLY trial), *atabecestat* resulted in a dose-dependent worsening of cognition and neuropsychiatric symptoms after only 3 months of treatment. Patients recovered after 6 months, but drug development was interrupted due to hepatic toxicity concerns [120].

10.4.1.2 Verubecestat (MK8931)

Verubecestat strongly and selectively inhibits the BACE1 enzyme, thus decreasing the production of Aβ peptide and preventing the deposit of amyloid in plaques. The drug was well tolerated in phase I clinical trials, with more than 90% reduction of Aβ in animal models' CSF, plasma, and cortex. It also achieved ≥90% reduction of $A\beta_{40}$, $A\beta_{42}$, and sAPPβ in healthy human volunteers [60].

In phase III RCT enrolling patients with mild-to-moderate AD, results showed no efficacy after 18 months of treatment [30]. Later, in another phase III trial with prodromal AD patients (confirmed by amyloid PET, but with no dementia), *verubecestat* performed worse than placebo concerning the clinical ratings after a 2-year period (APECS trial). Despite clearing amyloid plaques from the brain, the drug had no impact on cognition, even in mildly symptomatic AD subjects [31]. Adverse reactions, such as skin rash and hair color changes, falls, weight loss, and neuropsychiatric symptoms (sleep disturbances and suicide ideation), were more frequent in the treatment group. There was no association of *verubecestat* with amyloid-related imaging abnormalities (ARIA) [30, 31].

10.4.1.3 Lanabecestat (AZD3293)

Lanabecestat is a potent BACE1 inhibitor (nonselective for BACE1 vs BACE2) that consistently decreases $A\beta_{40}$ and $A\beta_{42}$ (approximately by 55–75%) as evidenced in phase I studies [18, 32]. In the phase II/III trials with MCI and mild AD (AMARANTH and DAYBREAK-ALZ, respectively), the drug failed to slow cognitive or functional decline over a 2-year period, with no differences in cognitive scores vs the placebo group. In respect to biomarkers, the AMARANTH study found considerable dose-related reductions in CSF $A\beta_{40}$ and $A\beta_{42}$ and of Aβ neuritic plaque density in the treatment arm, but also of the hippocampal volumes (the relevance of this finding is not clear). Although well tolerated, patients treated with *lanabecestat* developed a dose-related increase in psychiatric symptoms and also hair color changes and weight loss. There was no increase in microhemorrhages or vasogenic edema (ARIA). Both studies were halted for futility in interim analysis [137].

10.4.1.4 Umibecestat (CNP520)

Umibecestat is a small-molecule active BACE1 inhibitor that reduces Aβ and Aβ plaque deposition in the brain and CSF of animal models. It shows high brain penetration and no possible toxic metabolites. Treatment of healthy adults also resulted in dose-dependent Aβ reduction in CSF. The drug has been designed to have a selective BACE1 affinity, thus avoiding side effects evidenced with other compounds related to off-target binding (BACE2 and CatD), such as raise in liver enzymes, ocular toxicity, and hair depigmentation [19, 60, 77].

Two ongoing phase II/III clinical trials from the *Generation Program* (GENERATION and GENERATION2) are testing *umibecestat* on a cognitively preserved population with increased risk of AD based on age and ApoE4 genotype. Dosing was interrupted in both trials due to cognitive worsening and more brain atrophy and weight loss in the treatment group, as evidenced in the interim analysis [90].

10.4.1.5 Elenbecestat (E2609)

The BACE1 inhibitor *elenbecestat* can reduce Aβ level in the CSF as shown in phase I trials with healthy volunteers, where Aβ levels dropped in a dose-dependent manner by 62–85% when compared to placebo. Similar results were obtained in a phase II trial with MCI and mild AD, where Aβ in CSF decreased around 69% with treatment. Later, *elenbecestat* was assessed in two phase III RCTs with patients with MCI and mild AD dementia (MissionAD1 and MissionAD2). After 12 months of treatment, there was no evidence of benefits, but the side effect profile was worse than placebo, and the studies were terminated [102].

10.5 Other Perspectives

10.5.1 Tau-Based Therapies

Evidence reveals that tau-altering pharmacologic interventions would be worthwhile since tau pathology is more associated with clinical and cognitive decline, and tau may accumulate earlier [13, 86]. In addition, tau-directed immunotherapies have been developed based on the recognition that NFTs, synapse loss, and neuronal death are associated with clinical deterioration in AD [122]. Studies of tau-based therapies involve anti-tau antibodies and active immunization, tau antiaggregants, tau kinase inhibitors, and gene therapy [47]. The main objectives of these strategies are the reduction of tau oligomer levels, prevention of tau aggregation, and blockage of hyperphosphorylation or microtubule destabilization [51]. Amyloid-based therapies are more effective in the preclinical stages of the illness, take a long time to show significant results, and require more subjects than in trials of prodromal and mild AD [97, 99]. Tau interventions are supposed to be more effective in symptomatic patients and more likely to show benefits in patients at more advanced stages of the disease, representing that clinical trials could require smaller samples, at lower cost, and less time to show results. Finally, anti-tau approaches may be employed in other neurodegenerative diseases in which tau deposition occurs, such as PSP and frontotemporal dementia (FTD).

10.5.2 Lithium

Although the therapeutic use of lithium in psychiatric conditions dates back to 1949 [17], it was only in 1974 that the drug received FDA approval for the prophylactic treatment of bipolar disorder, and no study that assessed its efficacy versus a control group was published until 1994 [14]. After almost a century, the body of evidence from studies with bipolar disorder patients, in addition to a few trials with AD patients, supports the potential use of lithium as a disease-modifying treatment for neurodegenerative conditions [33, 61, 83].

Increased levels and activity of *glycogen synthase kinase 3 beta* (GSK3β) are an early pathological event in AD, triggering several downstream events and culminating with an increased production of Aβ and tau hyperphosphorylation. Lithium is known to inhibit GSK3β activity, with consequent reduction in tau phosphorylation and Aβ production [58]. Another key element in understanding the possible therapeutic effect of lithium in patients with AD concerns its action enhancing autophagy through the inhibition of *inositol monophosphatase* (IMP) and *inositol polyphosphate-1* (IPP) [54]. The reason why autophagy is aberrant in neurons of patients with AD is not fully understood, but since this mechanism is important to cellular homeostasis and synaptic plasticity (learning and memory), it is considered a potential target for treatment interventions [41]. Lithium treatment can also stimulate

brain-derived neurotrophic factor (BDNF) synthesis and release and hippocampal neurogenesis [140].

Hence, the rationale for lithium use in neurodegenerative disorders is explained by its combined effects in multiple intracellular signaling systems, inhibiting apoptosis and promoting the synthesis of neurotrophic factors, thus favoring synaptic plasticity, neurite outgrowth, and neurogenesis [40]. Nevertheless, its potential disease-modifying properties when used in patients with AD were tested in a limited number of studies [70].

Terao et al. [125], in a retrospective study, found that patients treated with lithium exhibited significantly better cognition and memory when compared to those receiving other treatments [125]. Kessing et al. also found a reduction in dementia rates among patients on continuous lithium treatment [61]. In a cross-sectional study, Nunes et al. [83] demonstrated a lower incidence of AD between elderly bipolar patients chronically treated with lithium and patients who were not exposed or were minimally exposed to lithium during their lifetime (7% vs 19%).

Finally, Forlenza et al. [39] conducted a randomized controlled trial (RCT) in patients with amnestic MCI and found that long-term use of lithium can reduce phosphorylated tau levels in CSF, with concomitant cognitive and functional stabilization during treatment. Later, in a new RCT that also included patients with amnestic MCI, lithium was compared to placebo during the course of 2 years [43]. Target lithium plasmatic levels were between 0.25 and 0.5 mEq/L, a subtherapeutic range demonstrated to be enough to assure a good concentration of lithium in the brain. The results showed that the participants in the lithium group performed better when compared to placebo after 2 years of treatment, probably due to cognitive stabilization among lithium users versus a mild progressive decline in the placebo group. A trend also suggested that conversion from MCI to dementia was smaller among lithium users.

Nevertheless, it is important to notice that only a small number of controlled intervention trials have assessed the possible benefits of lithium among patients with AD, and future research is needed to determine whether lithium use could be a therapeutic alternative between neurodegenerative conditions, including AD ([39, [42, 49, 84]).

10.5.3 Other Mechanisms of Action

Although only in China, GV-971 (oligomannate) became the first drug approved for treatment of AD since 2003 by the National Medical Products Administration (NMPA, Chinese equivalent of the FDA) for improvement of cognition in patients with mild-to-moderate AD dementia not treated with cholinesterase inhibitors or memantine. During the phase III of the clinical trial, a significant drug-placebo difference on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was seen together with a trend toward a difference on the

Clinician Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The outcomes satisfied the requirements of the NMPA for approval. Studies suggest that oligomannate interfere with the dysbiosis of the gut microbiome, decreasing the secreted amino acids (phenylalanine and isoleucine) that stimulate proliferation of peripheral pro-inflammatory T helper 1 (Th1) cells, contributing to neuroinflammation [26, 136].

Trials with different mechanisms of action have been reported with limited results but representing new perspectives. Clinical trials of nabilone, a partial agonist of cannabinoid receptors 1 and 2 [51]; pioglitazone, based on the knowledge that increased insulin resistance promotes both Aβ deposition and tau phosphorylation; and idalopirdine, a serotonin 5-hydroxytryptamine-6 (5-HT6) antagonist, are significant examples. Regarding the latter, serotonin 5-HT6 receptor antagonists are capable of optimizing the treatment of AD in regard to the cognitive symptom when in combination with cholinesterase inhibitors. Idalopirdine was tested as adjunctive therapy to AChE inhibitors for symptomatic treatment of patients with mild-moderate AD. Idalopirdine was studied in a phase III clinical trial, in various dosages, as a combination treatment with donepezil and memantine (NCT01955161, NCT02006641, NCT02006654, NCT02079246). Although no improvement in cognition occurred, the combination had significantly improved ADAS-Cog scores compared with patients receiving placebo at some point of the study, making this pathway a significant research line [25, 36].

10.6 Conclusion

Population aging and the burden of AD with its high prevalence and great impact on the functional capacity of individuals emphasize the need for early diagnosis and development of more effective therapies capable of modifying the progression of the degenerative process. A new comprehension of the neuropathological changes of AD is emerging. Considerable evidence from the last decades' research indicates that the accumulation of abnormally folded Aβ and tau proteins in amyloid plaques and NFT plays a pivotal pathophysiological role in neurodegenerative disorders such as AD. This sequence of events that culminate with AD is known as the amyloid cascade hypothesis – the amyloidogenic pathway – in which the APP is sequentially cleaved to a neurotoxic peptide, the Aβ42.

The impact of the biomarker-based classification system proposed in 2018 reveals a broader understanding of the disease's pathological process, and this new perception on biomarker and drug development studies is already causing significant changes and guiding the new perspectives seen in this chapter. However, clinical trials still face significant challenges in identifying the best molecular target or combination and developing better protocols to assess intervention outcomes. The main objective of detection of preclinical AD is to facilitate early therapeutic intervention, which is the premise underlying most of the new therapies studied.

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