Chapter 1
Introduction

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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

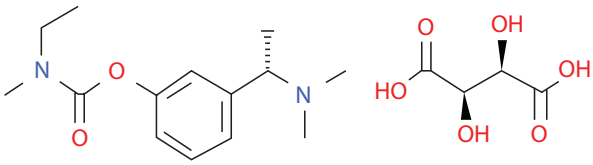

Fig. 1.1 Rivastigmine tartrate. (Source: Chemspider, 2021 [32])

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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