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**Neurodegenerative Diseases: from the First CNS Drugs to New Treatments in Discovery
(A Review)**

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Abstract—Man has always sought to eradicate pathologies that affect the CNS (pain, anxiety, insomnia, euphorants, psychedelic drugs, etc.). This obsession with finding new molecules that act on the CNS, has been considerably amplified by the increasingly frequent appearance of neurodegenerative diseases which affect human health. It is predicted that the world-wide prevalence of Alzheimer's Disease dementia, will triple from its current 50 to 150 million by 2050. The first part of this manuscript is a brief history of the discovery of the first molecules acting on the CNS. The second part describes drugs that are actually prescribed for the treatment of AD, unfortunately, these drugs have only low effectiveness on the disease, or even no observable effects. The third part describes current advances in the field of therapy of CNS-related diseases. Three research directions are currently in development: research for new innovative “small molecules” or resulting from a repositioning of molecules having received marketing authorization; development of monoclonal antibodies for the treatment of neurodegenerative pathologies; development of specific treatments such as neurostimulation for the treatment of Parkinson's disease; the last part of the manuscript is devoted to the Human Brain Connectome Project (HBCP), which aims to better understand the biological mechanisms of these neurodegenerative pathologies, and to help in the development of new treatments.

Keywords: Alzheimer's disease drugs , CNS drugs discovery, monoclonal antibodies, Human Brain Connectome Project (HBCP)

Running title: *Update on CNS drugs*

Abbreviations: AD, Alzheimer disease; AI, Artificial intelligence; CNS, Central nervous system; PGs, Prostaglandins; COX, Cyclooxygenase; BDZ, Benzodiazepine; FDA, Federal drug agency; IQ, Intelligence quotient.

1. HISTORICAL REMINDERS: DRUGS OF THE MERCY AND DRUGS OF MYSTICISM

At all times, man has sought to protect himself against pain, whether physical or psychological. It must be recognized that since the discovery of one of the oldest drugs described in the history of

chemistry, morphine, and more generally the opiates series constitute one of the major discoveries of the CNS drugs pharmacopoeia still in use today. Homer [1] in the Odyssey recounts the anguish of Penelope who still hopes for the return of Odysseus. Harassed by her companions in duty to choose a new husband to reign over Ithaca, she postpones the moment of choosing indefinitely. According to ancient Greek historians specialists, to calm her companions anxiety, Penelope recommended them, to take a potion which probably contain plant opiates derived from the opium Poppy, a flowering plant in the subfamily *Papaveroideae* of the family *Papaveraceae* (Poppy seeds contain small quantities of both morphine and codeine which are pain-relieving drugs) [2].

Even Cleopatra supposedly took sleeping pills, while her husband, general Marc Anthony, was away on a trip [3]. Shakespeare was one of the authors who best described a man's yearning for escape from tension. Let us remember Macbeth's request to his physicians to synthesize "*sweet oblivion's antidote, which cleanse the stuffed bosom, of that perilous stuff which weighs upon the heart*" that would allow him to remove the problems written in his brain [4]? The identification and the chemical structure of morphine, was determined by 1925 by Robinson [5].

Morphine has a highly challenging chemical structure, it is a pentacyclic tertiary amine (alkaloid) with 5 stereogenic centers and exists in 32 stereoisomeric forms. The desired analgesic activity resides exclusively in the natural product, the (-)-enantiomer with the configuration (5R, 6S, 9R, 13S, and 14R) [6].

Besides the major discovery of *morphine*, *aspirin* another drug highly active on CNS still widely used in the world has been discovered [7, 8].

In 1893, a Bayer chemist named Hofmann reinvestigated the acetylation reaction of salicylic acid, in the hope that the product might provide a less obnoxious method for relieving the sufferings of his rheumatic father. His hopes were borne out, and the Bayer company had a new product. Aspirin (acetylsalicylic acid) still plays a major role in the pharmacopoeia, and is still part of the therapeutic arsenal used to combat CNS conditions (headaches, acute pain, etc.). Aspirin is available in different formulations (*aspegic*, *kardegic*) in which acetylsalicylic acid is still the major ingredient. How does aspirin work on the molecular model, was discovered only after several years of its discovery? In 1971, Vane [9] discovered the mechanism by which aspirin exerts its anti-inflammatory, analgesic and antipyretic actions. He proved that aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme called cyclooxygenase (COX) which leads to the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever.

2. CURRENT CLINICAL DRUGS USED FOR NEURODEGENERATIVE DISEASE TREATMENTS

Besides those two old types of efficient drugs (Morphine and Aspirin), numerous other CNS active drugs have been discovered during the 20th century.

A large pharmacopoeia of natural or synthetic products acting on CNS is available to patients—drugs

that affect mental processes: Morphine, Aspirin, Cocaine, Barbitol, Δ -9-tetrahydrocannabinol (THC), Mescaline, Lysergic Acid (LSD), Psilocybin.

Some of these drugs extracted from plants, (coca leaves, mushrooms, cannabis, and hashish) act as mind changers; they allow the consumers to feel ecstasy of heaven, while other act as tranquilizers, sleeping pills, and even truth serums. Unfortunately, none of these drugs are effective against AD, an irreversible loss of memory function with no hope of return [10].

Today the trend of people affected by nervous system disorders is the use of various and varied active ingredients: feel tense? Take a pill. Can't sleep? Take a pill. People partake of energizers, sedatives, analgesics and even hypnotics in order better to cope with their pressure-filled lives. Despite the addictive effects of the drugs (Morphine, Aspirin, Cocaine, Barbitol, Δ -9-tetrahydrocannabinol (THC), Mescaline, Lysergic Acid (LSD), Psilocybin), even if these drugs are illegal in certain countries, these drugs are still widely used and their market constitute a flourishing parallel economy. Alongside these various illegal drugs, the discovery of the benzodiazepine family has taken a considerable place in treating the various pathologies of the CNS. Benzodiazepines (BZD) colloquially called "benzos," are a class of depressant drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. Most prescribed Benzodiazepines (antidepressant drugs)—Clonazepam (Rivodril), Alprazolam (Xanax), Lorazepam (Ativan), Diazepam (Diazepam).

Besides diazepam (valium) which is one of the most prescribed diazepine globally, other benzodiazepines drugs such as Xanax, Rivodril, and Ativan are actually largely prescribed to patients suffering of anxiety disorders, insomnia, and seizures [11, 12]. Diazepam discovered in 1963 [13] is among one of the most prescribed diazepine globally. Unfortunately, despite all the new CNS drugs recently discovered, none of them can cure or delay the evolution of AD, one the most disabling disease which affect populations all over the world without exception. There are over 55 million people worldwide living with dementia in 2020. This number will almost double every 20 years, reaching 78 million in 2030 and 139 million by 2050 [14].

Several specific drugs are prescribed to patients suffering of AD, or other related diseases. Among these drugs, Exelon, Aricept, Valos, Razadyne, Resveratrol approved by FDA and the European Drugs Agency (Agence Européenne du Médicament) are the most prescribed (Fig. 1).

Figure 1

Unfortunately, those drugs are ineffective against severe AD, or only slightly active on the evolution of the AD disease, in reducing or controlling some cognitive and behavioral symptoms. One of the most recent drug prescribed is Brexpiprazole (sold under the brand name Rexulti) which is a medication used for the treatment of major depressive disorder, schizophrenia, and agitation associated with dementia due to Alzheimer's disease [15]. The whole drugs have been approved for neurodegenerative diseases treatment and in particular for Alzheimer's disease [16].

Faced with this situation, we are forced to make the following observations: after 413 therapeutic trials carried out on AD patients between 2002 and 2012, no breakthrough has been observed [17], for the same period of time, the success rate reached 20% for oncology [18]. The following FDA approved drugs, have been shown to be active against different types of cancer (Imatinib, gefitinib, erlotinib, lapatinib, sorafenib, abiraterone, crizotinib, vemurafenib, and other new allosteric kinase inhibitors [19]).

Building on this observation of failure, the search for new molecules and new treatments for neurodegenerative diseases has progressed significantly. Drug makers and physicians specialize in CNS drugs and treatments were concerned about this lack of new drugs and treatments. Today many innovative molecules and different treatments are in the pipeline waiting to be developed. Already new treatments for AD may become available in the foreseeable future.

3. SMALL CNS DRUGS IN DEVELOPMENT

According to Cummings [20], in 2022 year there were 143 agents in 172 clinical trials for AD. The pipeline included 31 agents in 47 trials in Phase 3, 82 agents in 94 trials in Phase 2, and 30 agents in 31 trials in Phase 1. It should be recalled that of the 49 novel drugs approved by the FDA in 2021, seven were for treatment of disorders of the central nervous system and two were for the peripheral nervous system disorders such as *Duchenne muscular dystrophy* and *myasthenia gravis* [21].

It should be underlined that Diseases Modifying Therapy (DMTs) are the agents most included in the pipeline. One hundred nineteen putative DMTs are being assessed (21 in Phase 3, 71 in Phase 2, 27 in Phase 1). DMTs represent 83.2% of the pipeline of agents. There are 14 cognitive enhancers and 10 drugs targeting neuropsychiatric symptoms in the pipeline. There are 143 agents in the pipeline compared to 126 in the pipeline in 2021 [22, 23].

There is no question of giving in this manuscript the whole molecular structures of drugs currently in development, nevertheless among the new prescribed drugs, two new drugs Brexpiprazole and Suvorexant (Fig. 2) emerged since they are prescribed for their specific CNS activities: *Brexpiprazole* sold under the brand name Rexulti, has demonstrated efficacy and safety, mainly for the treatment of major depressive disorder, schizophrenia and agitation associated with dementia, due to AD [24]; Suvorexant sold under the brand name Belsomra [25] is mainly used to reduce AD patients' insomnia.

In 2023, the two drugs have been approved for neurodegenerative diseases treatment and in particular for Alzheimer's disease [16].

Figure 2

4. NEW TREATMENTS FOR NEURODEGENERATIVE DISEASES

4.1. Monoclonal Antibodies

Development of new Monoclonal Antibodies could be a hope for AD treatment. Quite recently, it has been shown that anti-amyloid monoclonal antibodies could represent the first disease-modifying therapies for AD. The antibodies help the clinical decline of AD patients by intervening in the basic biological processes of the disease. These antibodies anti amyloid, could represent a breakthrough for AD therapy in slowing the inevitable progression of AD into more severe cognitive impairment.

These new drugs work directly on what may cause the disease, instead of just the symptoms. They target the protein fragments that build up in your brain and form plaques, a defining feature of the disease.

Among this new class of antibodies recently FDA approved Aducanumab, sold name under the brand name *Aduhelm*. This human IgG1 mAb antibody, targeting amino acids 3–7 of the α , β -peptide, is specific for $\alpha\beta$ -plaques [26–29]. On 7 June 2021, the US Food and Drug Administration approved aducanumab for the treatment of Alzheimer’s disease [26, 27]. More recently a new monoclonal antibody Lecanemab, sold under the brand name *Leqembi* [30] has been approved for medical use in the United States in January 2023, and fully approved by the FDA in July 2023 [31, 32].

This antibody represents a new hope for the treatment of Alzheimer’s disease [24, 25]. Both Aducanumab and Lecanemab, are amyloid beta-directed antibody, given via intravenous infusion. Lecanemab is the first antibody to clearly slow cognitive decline in patients with early-stage disease, fueling excitement in the Alzheimer’s field and hope for patients and families. The most common side effects of Lecanemab include headache, confusion, dizziness, vision changes, nausea and seizure infusion-related reactions and amyloid-related imaging abnormalities, a side effect known to occur with the class of antibodies targeting amyloid [33].

At present time, nobody knows clearly if the use of monoclonal antibody remains an important way to treat AD patients, the question of the validity and effectiveness of these drugs remains in question. We need more time to know what is going on with the monoclonal antibody treatment, as already mentioned side effects of monoclonal therapy are numerous and quite serious.

Nevertheless, actually 7 monoclonal antibodies, 1 active vaccine, 1 ASO (Allele-Specific Oligonucleotide (ASO)), and 4 small molecules directed at aspects of the biology of the tau protein and neurofibrillary tangle formation, are currently in AD clinical trials. In contrast several tau monoclonal antibodies have failed to establish a drug–placebo difference in recent AD trials including Semorinemab, Zaganemab, Gosuranemab, and ABBV-8E12 [34, 35].

4.2. Neuro Stimulation Treatment

According to World Health Organization (WHO) [36] 25% of the world’s population are affected by mental disorders at some point in their lives, neuro stimulation appeared in 2010 as a promising treatment for Parkinson’s disease patients. This treatment involved stimulation of specific

parts of the brain from the outside of the skull via an electric current or magnetic field. Unfortunately, very little is known about the links between the effect of chemicals molecules and neurostimulation [37]. Moreover, not all patients with Parkinson's disease are eligible to this High-Frequency Deep Brain stimulation (DBS) of the subthalamic nucleus (STN-HFS) [38, 39].

5. THE HUMAN BRAIN CONNECTOME PROJECT

Similarly, to the human genome project at its time [40], Human Brain Connectome Project [41, 42] (HBCP), launched in 2009, is an ambitious effort to map the neural pathways that underlie human brain function. The purpose of this project is to acquire and share data about the structural and functional connectivity of the human brain. The HBCP project is important, because for the first time, researchers combined different brain imaging technologies to map the brain's long-range connections systematically. This research paved the way for a deeper understanding of how our brain circuitry changes as we age or because of psychiatric and neurologic conditions [43].

The Human Brain Connectome Project (HBCP) is an ambitious effort to: accelerate advances in human neuroimaging, particularly for measures of brain connectivity; apply these advances to study a large number of healthy young adults; freely share the data and tools with the scientific community.

In just over 6 years, the HBCP consortium succeeded in its core objectives, thanks to the help of 64-bit computers with clock running around 4GHz, which perform 10^{13} logical operations per second. These computers could compete with the train human brain of 10^{11} neurons, each of which switches more than 100 times per second [44].

One has to remember that in thirty years Artificial Intelligence (AI), is going to have an Intelligence Quotient (IQ) of 10000, for comparison, the average human IQ is 100 and a genius is around 200 [45]. The functioning of the cortex is based on the involvement of complex neural networks. The exact knowledge of anatomical and functional organization of these networks is therefore decisive for a better understanding of cortical functions. However, this task is made very difficult because of the number and variety of neurons that make up these networks and because it is necessary to understand how each cell type integrates into the heart of cortical circuit. The human brain is made up of about 170 billion cells, including 86 billion neurons on average which form around 60000 synapses. That is about $6 \cdot 10^{14}$ synapses which can be controlled by the brain [46].

CONCLUSIONS

Man's unending search for life's meaning, for deep psychological satisfactions, and for insights into immortality, have led him to collect, catalog and even concoct substances that allow him to transcend normal physical limitations. Centuries have separated the discovery of Morphine or Aspirin. Today AD drug development pipeline is leading to new CNS therapies. After a 17- year hiatus in drug approvals, two monoclonal antibodies—aducanumab and lecanemab—have entered the market since 2021; Brexpiprazole ameliorated agitation in a Phase 3 AD trial; and Suvorexant reduced

insomnia in AD in a Phase 3 trial [47] . Aducanumab and lecanemab are the first DMTs for AD and among the first DMTs for any neurodegenerative disease [48, 49]. Both agents were approved by the FDA. The recently approved therapies provide treatment for a relatively limited segment (e.g., early AD) of the large and growing AD population. They represent initial steps in the march toward more comprehensive treatments with multiple therapeutic options for those with or at risk for AD.

Man has always sought to protect himself against physical and moral pain. Since the discovery of opiates, many centuries ago, the search for new treatments for brain diseases continues to evolve. Today, the research is at the point that in parallel with the search for new molecules and new treatments, man has taken on the challenge, to map the brain neural networks in order to understand how the brain works in the hope to find new treatments to cure these neurodegenerative diseases which constitute the greatest scourge threatening human health worldwide.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals performed by any of these authors.

CONFLICT OF INTEREST

Author declare that they have no conflict of interest.

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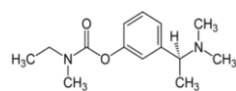
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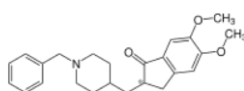
Figure

Legends

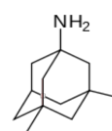
Fig. 1. Drugs actually prescribed for AD treatment.



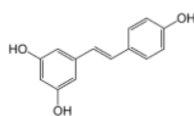
Rivastigmine (Exelon)



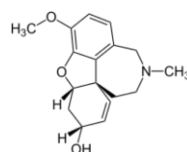
Donepezil (Aricept)



Nemantine (Valos, Exiba)

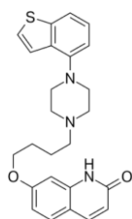


Resveratrol

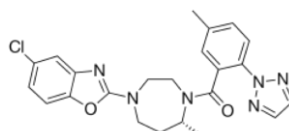


Galantamine (Razadyne)

Fig. 2. CNS drugs recently FDA approved.



Brexiprazole



Suvorexant