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Review Article

Impacts of Drugs on Alzheimer's Diseases

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Abstract

In 1901, Alois Alzheimer first reported Alzheimer's disease. It is a disease that destroys memory and other essential mental functions mostly observed in an older person and mainly in women. Various treatment techniques have been used, which involve Ayurveda, homeopathy, modern drugs, etc. Turmeric, Ashwagandha, Brahmi, Ghrita, etc. are some ayurvedic medicines used to cure this disease, but they were relatively slow in processing. Drugs like Donepezil, Galantamine, and Rivastigmine are speedy, and thus they are in the market nowadays. In this review article, we will give information and awareness about the drugs therapy used for disease treatment and their effects.

Keywords: Alzheimer's disease; Ayurveda; Homeopathy

Introduction

In 1901 Alois Alzheimer, a psychiatrist, discovered the first case related to this. The patient named Auguste D., a 50 years old German lady's case, was followed by Alois until she died in 1906, and he reported publicly about this disease. Alzheimer's disease is a kind of Dementia that damages the brain cells [1]. The main symptoms are indecision and loss of memory. There are in total, seven stages that get worse with time (Figure 1).

According to the Global Burden of Disease Study in 2015, approximately 29.8 million people worldwide with Alzheimer's disease. In India, 5-6% of people aged 65-70 years suffer from this disease. Among all, the USA has an immense death rate with 5.5 million people of all ages. This death rate is shown in the following chart (Figure 2).

Traditional medicines, which are natal to India, like Ayurveda, gave many medicines related to this disease for the treatment but later proved to be stagnant, and other than Ayurveda herbal, homeopathy be slow. Various modern drugs like Donepezil, Memantine, Solanezumab have been come into existence to treat Alzheimer's. However, currently, no drugs are available to halt the progression of neurodegeneration in Alzheimer's disease; the nature of Alzheimer's disease treatment is symptomatic [2]. Memantine, an N-methyl-D-aspartate (NMDA) receptor adversary, is used in moderate to severe cases to stop excitotoxicity, and antipsychotics and antidepressants are used to treat neuropsychiatric symptoms [3,4]. There are mainly two types of assistances a) acetylcholinesterase inhibitors, b) N-methyl D-aspartate antagonists. Both the techniques differ from each other. The detailed mechanisms of drugs and their effects on Alzheimer's disease are explained further in this article.

Understanding Alzheimer's

Alzheimer's is a disease that is irreversible and shatters the memory and even the ability to do the most straightforward task. It slowly destroys the brain cells, especially those areas of the brain that control thinking skills, memory, and language. In some cases, Alzheimer's can be caused by a gene mutation that passes from parent to child. Alzheimer's includes seven main stages: a) first two stages involve normal behavior, and we cannot detect the person is having disease unless and until a PET scan (scanning of brain tissues) is done. b) The third stage is when one can start recognizing the patient's symptoms, which can be forgetting what he/she read recently or asks the same question again and again. c) In the fourth stage, the symptoms observed in stage three get more expressive. The symptoms involve forgetting which date or month is going on, forgetting details about himself, or writing everyday things like dates. d) In the fifth stage, the patient can start losing track of where he is or what time is. The patient also starts slipping his address, phone numbers, e) the Sixth stage is the severe decline stage where the symptoms involve; the patient recognizes the face but forgets the name, he also forget the relations like he recognizes his father as his brother. f) In seventh stage patient dims his essential ability of eating and walking. In this stage, the patient forgets that when he is thirsty, what he was doing, etc. People can die by infection or blood clots during this disease. Many ayurvedic medicines and modern medicines have discovered many medicines to cure this, further explained here.

Ayurvedic medicines

Ayurvedic medicine is a system of traditional medicine vernacular to India, and ayurvedic practitioners have developed many medicinal preparations and surgical procedures for the treatment of numerous diseases [6]. Some ayurvedic medicines used for the treatment of AD are Turmeric, Ashwagandha. Turmeric is used as a coloring agent, traditional medicines, and spice in Asia. The primary and active constituents are water-soluble curcuminoids, including curcumin and turmerone oil. Curcumin is the principal curcuminoid and is responsible for the yellow color of turmeric roots [7]. Some studies indicate that the nonsteroidal anti-inflammatory property of turmeric is associated with the reduced risk of AD [8]. When given to transgenic mice, it reduced oxidative damage and reversed the amyloid pathology in AD [9]. After looking at the positive results in animal models, patients with early AD clinical trials of oral Curcumin are already commenced. Ashwagandha is an evergreen shrub that is mainly found in India and is also called Indian ginseng or Winter cherry, and the name is described from the smell of its root, i.e., as a horse. The calming effect on the Central Nervous System (CNS) by the extract of Ashwagandha root on several mammalian species indicates

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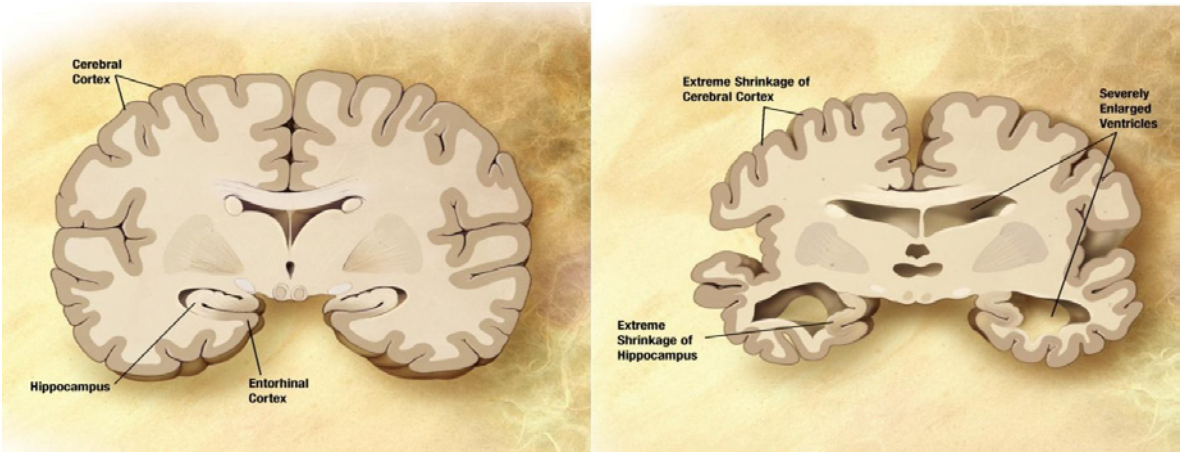

Figure 1: Effect of Alzheimer's disease on the brain [1].

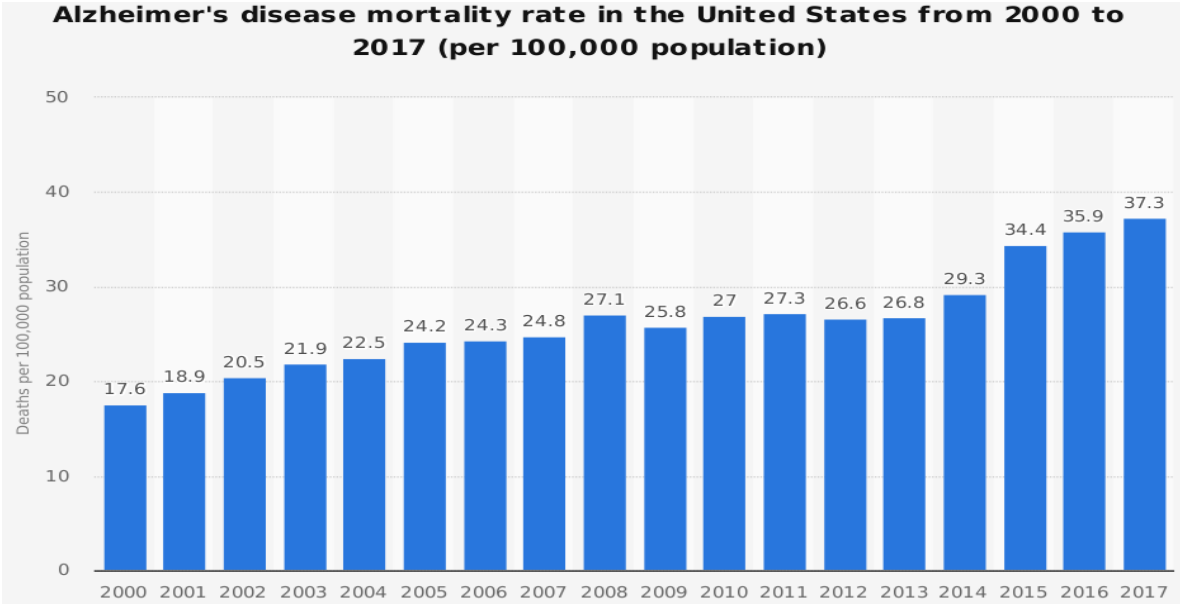

Figure 2: Alzheimer's disease mortality rate in the United States from 2000 to 2017 [2].

the use of Ashwagandha to produce relaxation. Withanolides A to Y, withasomniferin-A, withasomidienone, dehydrowithanolide-R and withasomniferols A to C are some ergostane types of steroidal compounds, which can be found in Ashwagandha. Ashwagandha is reported to increase memory and to learn in CNS. Aqueous extracts of this shrub have enlarged cholinergic activity, including increases in the acetylcholine content and choline acetyltransferase activity in rats, which might partially explain the cognition-enhancing and memory-improving effects [10,11]. Ashwagandha can be used as an anti-AD agent, but supplemental clinical trials are needed to be conducted to assist its therapeutic use. Bypassing the Blood-Brain Barrier (BBB) is a substantial challenge to medicine delivery into CNS. BBB prevents many therapeutic agents from treating brain-related diseases or injuries, including AD, brain tumor and head injury.

Ayurveda depends on some novel methods of administrating herbs or their predations or both to treat CNS disorders. [6] Nevertheless, research and studies lack that these herbs or shrubs should be given orally or by some other means to cross BBB and reach CNS.

Neurodegenerative pathways involved in AD

Several mechanisms explain the pathology of AD; both current and potential future treatment is based on the modification of these pathways (Figure 3).

Amyloid hypothesis: The amyloid hypothesis of AD gained attraction in the 1990s and centers on abnormal processing of the amyloid precursor protein (APP), which leads to the production of amyloid-beta (Aβ) [12]. Mutations in gamma and beta- secretases due to APP, divided by secretase enzyme, can lead to the abnormal production of amyloid-beta. Thus, it leads to synaptic damage and neuron loss. The official pathological marks of AD eventually include neurofibrillary tangles (NFTs) and amyloid plaques composed of

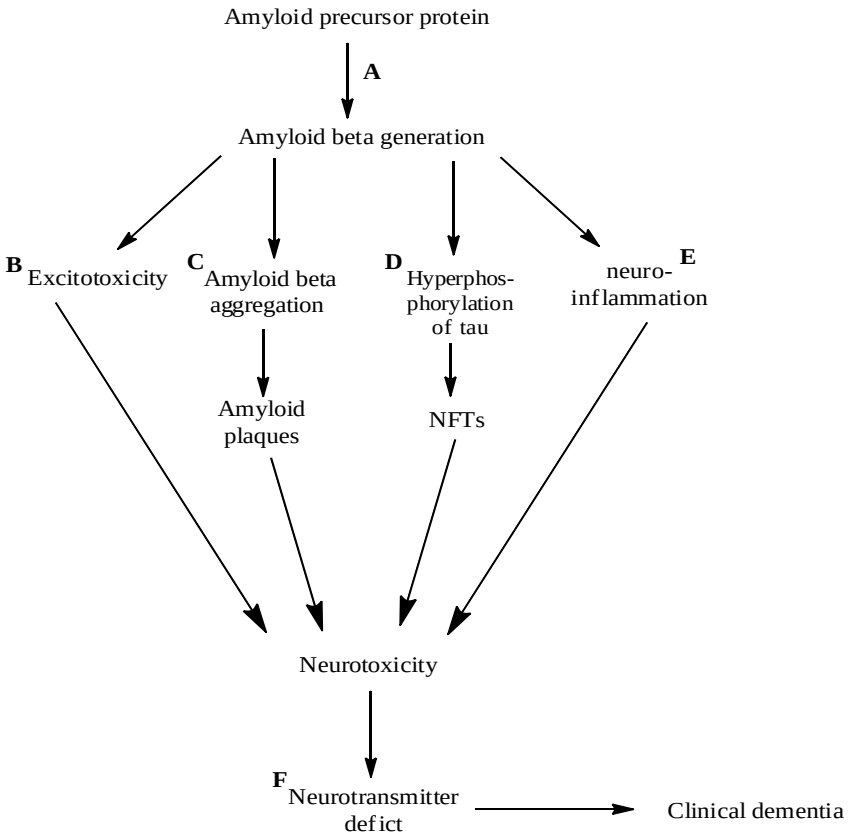

Figure 3: Aetiology of Alzheimer's disease with therapeutic targets.
Where A) Secretase enzyme inhibitor; B) NMDA receptor modulator; C) Immunotherapy; D) Anti-tau therapy; E) Anti-inflammatory treatments; F) Anticholinesterase inhibitors, e.g. Donepezil.

hyperphosphorylated tau protein in neurodegeneration.

Cholinergic hypothesis: Initial progress in AD came in the 1970s with the demonstration of a cholinergic deficit in the brains of patients with AD, intervene by deflects in the enzyme choline of patient's acetyltransferase [13]. Acetylcholine has a role in memory and learning. It led to the cholinergic hypothesis of AD, prompted to increase cholinergic activity therapeutically.

Tau hypothesis: Tau is a kind of protein that is responsible for modulating the stability of axonal microtubules. This protein is assembled into NFTs masses present inside the nerve cell bodies; this happens because of hyperphosphorylation and thus prevents them from accomplishing their normal functions. Hyperphosphorylation takes place downwards of Aβ, with research suggesting that assembling of Aβ may initiate this process [14].

Excitotoxicity: Excitotoxicity is defined as overexerts to the neurotransmitter glutamate, of overstimulation of its N-Methyl-D-Aspartate (NMDA) receptor, plays a vital role in the continuous neuronal loss of AD [15]. The loss of cholinergic neurons is afflicted by this process, which results in an enormous influx of calcium into cells.

Drug Therapy

Past few decades, most of the research in AD has been directed towards disease-modifying therapy that alters the course of the disease instead of acting on symptoms alone. However, the lack of effective disease-modifying drugs arising from these studies emulates the challenges involved in developing therapeutic agent with the potential to modify the course of a disease as complex as AD [16]. Some of the approved drug treatments are explained below.

Cholinesterase inhibitors

Tacrine was the first generation cholinesterase inhibitor but became finite because of hepatotoxic side effects [17]. Rivastigmine, Donepezil, galantamine are some drugs that are extensively used nowadays. The strength of these drugs is almost equal so that the selection can be based on the physician's experience, tolerance of an individual, and costing.

The mechanism of action of Donepezil is that it reversibly binds with acetylcholinesterase, which obstructs the hydrolysis of acetylcholine. It increases the opportunity of acetylcholine at synapses, augments the cholinergic transmission. Initially, Donepezil is prescribed with the dose of 5mg in the evening or at night, increasing to 10mg after one month if appropriate [18]. Donepezil is always given at night because it almost causes irregular or slow heartbeat for some of the patients, which causes fainting, so when given at bedtime, patients can sleep over those side effects. Common side effects observed due to Donepezil are fatigue, insomnia, vomiting, nausea, diarrhea, tiredness, poor appetite, etc.

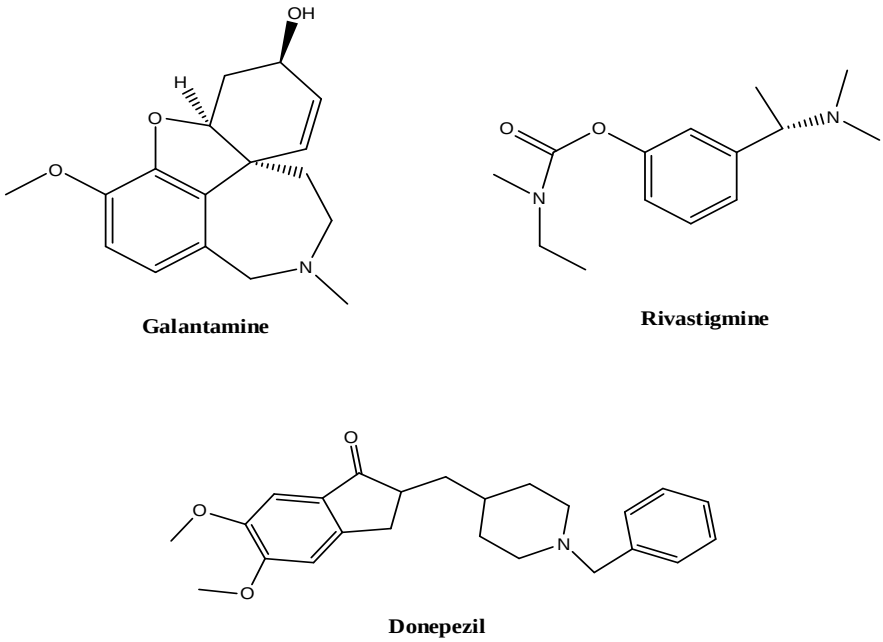

Figure 4: The structures of Galantamine, Rivastigmine, and Donepezil.

Table 1: The Information about the mechanism of drugs, their type, and typical side effects.

Name of the Drug	Drug's type and stage were used	Mode of Action	Side effects
Donepezil (Aricept)	Cholinesterase inhibitor used for mild, moderate, and severe Alzheimer's	Stops the breakdown of acetylcholine in the brain	Vomiting, diarrhea, fatigue, insomnia, etc
Rivastigmine (Exelon)	It inhibits both acetylcholinesterase and butyrylcholinesterase and is used for mild to moderate Alzheimer's (involves patches for severe cases)	Prevents the breakage of both acetylcholinesterase and butyrylcholinesterase present in the brain.	Tremor, weakness, nausea, weight loss, indigestion, etc
Galantamine (Razadyne)	Inhibitor of acetylcholinesterase and used to treat mild to moderate Alzheimer's	It holds back the breakdown of acetylcholinesterase and also stimulates nicotinic acetylcholine receptors to acquit more acetylcholinesterase in the brain	Fainting, dizziness, nausea, vomiting, diarrhea, dizziness, etc
Memantine (Namenda)	Does the blockage of the current flow of NMDA receptors and is used to treat moderate to severe Alzheimer's	Stops the lethal effects of excess glutamate	Hypertension, confusion, headache, constipation, etc
Memantine and Donepezil (Namzaric)	Cholinesterase inhibitor and opponent of NMDA and is used to treat moderate to severe Alzheimer's	It blocks the harmful effects of excess glutamate and prevents the breakdown of acetylcholinesterase present in the brain	Nausea, anorexia, headache, dizziness, etc

Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase. It is not selective like Donepezil, which inhibits only acetylcholinesterase. It is believed that there can be the breakdown of the brain neurotransmitter acetylcholine by inhibiting these cholinesterase enzymes. Initially, 1.5mg twice a day can be increased in steps of 1.5mg twice a day at the intervals of at least two weeks, depending on the tolerance and can be rose to 6 mg twice daily [18]. It can be taken orally as capsules or liquid by applying patches on the skin. Commonly observed side effects are tremors, weakness, etc. These can be diagnosed when taking medicine or when the dose is increased.

Galantamine is having a particular mode of action. It is the competitive inhibitor of acetylcholinesterase and is the only drug that is resolutely marketed for AD treatment with the confirmation as an allosteric modulator of nicotinic acetylcholine receptors. Dosage is 4mg orally every 12hrs and can be increased to 8mg each morning. Familiar side effects noticed are fainting, dizziness, nausea, vomiting, etc (Figure 4).

Memantine

The mechanism of action of memantine is the blockage of the current flow of NMDA receptors. It is a glutamate receptor involved in brain function. Memantine can be used to treat moderate to severe AD. However, it does not cure AD but improves the memory and ability to do daily work [19]. Initially, 5mg of daily dosage is provided and can be increased weekly by 5mg to the maximum dosage of 20mg. It is a drug with very few side effects like hypertension, confusion, headache, etc. Adding memantine to donepezil monotherapy may be advantageous for those having mid-stage AD [20]. Both Donepezil and memantine are not proven beneficial in the Medical Council of India (MCI).

Here is the table that provides information about the mechanism of drugs, their type, and typical side effects (Table 1).

Future in treating Alzheimer's disease

Immunization therapy, Drug therapies, Cognitive training, Monoclonal antibodies, etc. are the current clinical trial on which

Table 2: Some monoclonal antibodies and drugs are mentioned below with their results, mode of action, phases and limitations.

Name of Drug	Mode of Action	Result	Phase	Limitations
Bapineuzumab	Clearance of Aβ	In progress	3	Amyloid angiopathy
Rosiglitazone	Inhibition of β-secretase	Ineffective	3	Biomarker lacking
Methylthioninium chloride	Inhibition of tau aggregation	Clinical improvement (with 60mg per day)	2	Biomarker lacking

scientists are working.

Some monoclonal antibodies and drugs are mentioned below with their results, mode of action, phases, and limitations (Table 2).

Conclusion

The effect of some ayurvedic medicines and drugs are discussed here. Recent use of drugs in AD has improved effect and is promising, but they must be used with caution. The drugs available are used for curing symptoms but are insufficient, so scientists are working on the cure of AD. Many techniques like immunization therapy, cognitive training, and treatments for cardiovascular disease and diabetes on which our great scientists are engaged. Alzheimer's itself is a very complex disease by its nature, which needs universal access to care. Managing patients with AD is a tough job, but holistic care should be taken. In the future, many biomarkers can be used to predict the disease chain before the development of unconcealed AD.

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