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Review Article

Evaluating neurosurgical interventions versus pharmacotherapy in treating Alzheimer's Disease: A comprehensive review

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ABSTRACT

Alzheimer's disease is defined as a progressive neurodegenerative disorder, known to mainly affect the older human population. Its prevalence is strikingly increasing raising the social and economic burden and calling for new strategies in its treatment and research. Currently, the treatment branches into two main approaches: pharmacotherapy and neurosurgical procedures. Pharmacotherapy involves the administration of drugs that either target Ach esterases known to serve for the appearance of the hallmark accumulations or pharmacological, maybe natural or synthetic, substances that counter the damage and stress highlighted in the disease's pathophysiology. These include: acetylcholine esterase inhibitors, nanoparticles, neurotrophic and neuroprotective factors, in addition to drugs targeting the mitochondria and the associated inflammatory circuit. Neurosurgical procedures are techniques that involve direct manipulation of the central nervous system whether through invasive or non-invasive procedures. The techniques involve neuromodulation, active electrical stimulation, permeability changes in addition to administering vectors or tissue grafts. Some of the treatment neurosurgeries include: Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS), transcranial magnetic stimulation (rTMS), gene therapy, stem cell therapy and optogenetics. In fact, both approaches have undergone and still undergo extensive advancement to yield the safest, most effective and affordable treatment. In this review, we aim evaluate the current best available treatment approach basing our comparative analysis on four main criteria: effectiveness, safety, quality of life and cost-effectiveness. In the course of our analysis, we comprehend that pharmacotherapy is still safer, more affordable with proven good effectiveness. Neurosurgery is also promising and has a logical successful avenue in condition more clinical and translational trials are conducted to target safety and cost-effectiveness in addition to efficiency.

KEYWORDS: Alzheimer's Disease, pharmacotherapy, neurosurgical procedures, outcomes

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1. Introduction

Dementia, primarily caused by Alzheimer's disease (AD), is a progressive neurodegenerative condition that leads to cognitive decline and loss of independence. As the global population ages, dementia has become a major health concern, with a particularly sharp rise expected in older populations in China, India, and Latin America. By 2050, the global population aged 60 and older will increase by 1.25 billion, with most living in less developed regions [1]. Epidemiologically, AD affects older people with the likelihood of developing AD doubling approximately every five years after the age of 65 [2]. This disease shows a higher prevalence in women than in men, with nearly two-thirds of those affected being female, this gender disparity is thought to be influenced by several factors, including longer life expectancy in women and potential differences in hormonal and genetic risk factors [3]. Moreover, the incidence and prevalence of AD vary significantly across different cultures and geographic regions; higher rates have been observed in North America and Western Europe compared to Africa and Asia, likely reflecting differences in diagnostic practices, lifestyle factors, and genetic predispositions [4]. AD's etiology is multifactorial, involving a combination of genetic, environmental, and lifestyle factors with the age remaining the most significant risk factor [2]. Genetics also play a crucial role, particularly the presence of the APOE ε4 allele, which has been strongly associated with increased AD risk. Individuals carrying one copy of this allele have a three- to four-fold increased risk, while those with two copies may have up to a 15-fold higher risk [5]. Cardiovascular health is another critical aspect influencing AD risk. Conditions such as hypertension, diabetes, obesity, and hypercholesterolemia have been linked to a higher incidence of AD, likely due to their contribution to vascular damage and reduced cerebral blood flow [6]. Lifestyle factors, including physical inactivity, poor diet, and smoking, also contribute significantly to the risk profile [7]. Moreover, emerging evidence suggests that chronic neuroinflammation may exacerbate the disease's progression [8]. The clinical presentation of AD typically begins with subtle memory lapses and progresses to more severe cognitive impairment, including difficulties with language, problem-solving, and executive functions. Behavioral and psychological symptoms, such as depression, apathy, and aggression, often accompany the cognitive decline. In the late stages of AD, patients may lose the ability to communicate effectively, become bedridden, and require complete care [9]. The pathophysiology of AD is complex and involves several mechanisms that contribute to the characteristic neurodegeneration observed in patients. Central to the disease process is the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. The formation of Aβ plaques results from the abnormal cleavage of the amyloid precursor protein (APP), leading to the aggregation of Aβ fragments in the brain's extracellular space [10]. Neurofibrillary tangles, on the other hand, develop intracellularly due to the hyperphosphorylation of tau protein, which disrupts the microtubule network within neurons, leading to cell dysfunction and death [11]. These pathological changes are closely associated with neuroinflammation, which is now recognized as a critical factor in AD progression. Chronic activation of microglia, the brain's resident immune cells, in response to Aβ plaques and tau tangles, leads to the release of pro-inflammatory cytokines and chemokines, further exacerbating neuronal damage [12]. Recent studies have highlighted the role of the NF-κB signaling pathway in neuroinflammation, suggesting that targeting this pathway could synchronize the function of nervous tissue progenitors and potentially offer therapeutic benefits [13]. Additionally, the dysregulation of metal ions, particularly copper and iron, has been implicated in AD pathology due to their role in oxidative stress and the promotion of Aβ aggregation [14]. Despite being a public health issue, currently, Alzheimer's disease has only two approved classes of drugs as a symptomatic non curative treatment: cholinesterase enzyme inhibitors and N- methyl D-aspartate (NMDA) antagonists [15]. Pathophysiologically speaking, acetylcholine (Ach) producing cells are destroyed by several mechanisms in AD, so inhibiting cholinesterase enzyme which breaks down Ach and decreases its level results in higher levels in synaptic cleft and thus treating the symptoms of this disease [15]. Moreover, high levels of influx calcium (Ca^{2+}) due to NMDA receptor over activity leads to neuronal death and synaptic dysfunction, thus NMDA antagonists can protect neurons from high levels of Ca^{2+} [15].

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On the other hand, many neurosurgical AD therapies have been attempted over the past 40 years like electrical neural stimulation, gene therapy, tissue grafts, intraventricular infusions, and CSF shunting in addition to novel procedures such as optogenetics and stem cell therapy [16]. Gene therapy and electrical neural stimulation among the listed therapies are beneficial treatment methods for AD in which they can affect neuronal activity and result in clinically useful developments in cognitive function [16]. In this review, we are going to evaluate the better choice of treatment whether it is pharmacotherapy or neurosurgery. So we will compare the two choices by reviewing their outcomes from the perspective of safety, efficacy, quality of life and costs.

1. Pharmacotherapy in the treatment of Alzheimer's Disease

Early Drugs in the treatment of Alzheimer

The pathophysiology of AD is attributed to aggregation of amyloid beta plaques, hyper phosphorylation of tau proteins, formation of neurofibrillary tangles, and microglial activation which all lead to synaptic toxicity, neuroinflammation, and neurovascular damage thus inducing cognitive decline [17]. Beta amyloid (Aβ) is mainly formed by the cleavage of amyloid precursor protein (APP). The cleavage of APP is done by β-secretase and γ-secretase [18]. Selenium plaque (SP) resulting from progressive accumulation of parenchymal amyloid plaque due to mutation in APP or in β-secretase enzyme accumulate in hippocampus and entorhinal cortex that are responsible for memory [19]. The cascade of amyloid plaques leads to neurofibrillary tangles and hyper phosphorylated tau proteins resulting in neurodegeneration. Tau are proteins that normally function in stabilization of cell cytoskeleton [20]. The accumulation of amyloid plaque, and tau hyperphosphorylation induce the cytokines release to the affected area increasing the cerebral blood flow to remove damaged tissues with microglia [21]. This excessive inflammatory response leads to chronic inflammation and neuronal death [19]. Cholinergic neurotransmission plays a vital role in enhancing the cognitive function in AD by countering the accumulation of beta amyloid, and the cholinergic treatment shows a high efficacy in therapy for mild to moderate AD cases. Acetylcholine is degraded in the brain by two enzymes the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). AChE and BChE cholinesterase inhibitors prevent the degeneration of acetylcholine in synapses increasing its level [22]. Despite the wide socio- economic costs and plenty of research specialized in drug for treating AD still most of drugs cure symptoms rather than causes [19, 23]. The most common drugs used for symptomatic treatment are cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine), or neuroprotective as N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) [24].

Tacrine

Tacrine, a cholinesterase inhibitor, is the first drug approved in 1993 but it got banned in 2013 due to its hepatotoxicity and its side effects including nausea, vomiting, dizziness, diarrhea, seizures, and syncope [25]. It is a cholinesterase inhibitor that binds noncompetitively but selectively on central nervous system to trigger secretion of Ach, and activation of M1 subtype muscarinic receptor and suppression of M2 muscarinic receptors; raising nicotinic receptors activated at low and inhibited at high concentration [26].

Donepezil

Donepezil is approved in 1996 for mild to moderate cases [19]. Donepezil, a derivative of indanonebenzylpiperidine working on cognitive and behavior symptoms, is one of acetylcholinesterase inhibitors that reversibly inhibits acetylcholine hydrolysis inducing higher concentration of acetylcholine at synapse thus enhancing cholinergic transmission. It reduces neuroinflammation by activating microglia and astrocytes [27, 28]. The dosage form of Donepezil is found as tablets, liquid or transdermal, it is recommended to take it in 5mg increased to 10mg after one month and can reach 23mg, if it doesn't give any effect, it is better to stop it after third month. Its most adverse effect is gastrointestinal including nausea, diarrhea, and vomiting [20].

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Rivastigmine

Rivastigmine is pseudo-irreversible, brain selective inhibitor of acetylcholinesterase that was approved in 2000 [29]. It easily passes blood brain barrier and the recommended dosage is 1.5mg/12hr increased to 6mg/12hr after two weeks with the most effective dose being 3- 6mg/12hr. A transdermal dosage is used in patients unable to chew or swallow; the improvement in the cognitive function is shown after 26 weeks [30].

Galantamine

Galantamine, an alkaloid in the Amaryllidaceae family, is widely used in AD treatment and its approved since 2001 [25]. It is reversible competitive inhibitor that binds allosterically to α- subunit of nicotinic acetylcholine receptors and activates them [27]. Its treatment impact is on behavioral, cognitive and functional behavior symptoms of AD. The recommended dosage is 16- 24mg/day, it could be administered orally but may be taken intranasal to avoid the side effects including stomach ache, gastrointestinal disturbance, nausea and vomiting [31].

Memantine

One third of patients, who don't tolerate acetylcholinesterase inhibitors, take drugs that are antagonists with low affinity to N-methyl-D-aspartate (NMDA) receptors. Memantine is characterized by neuroprotective effect by restoring function of damaged neurons; it uncompetitively blocks the receptor with mild to moderate affinity by binding to cationic cochannel on these receptors thus inhibiting glutamate binding. This decreases the effect of glutamate and reduces its neurotoxicity [30]. Memantine which is especially used in treating moderate to severe AD, is recommended to start with 5mg/day then increase it to reach a maximum dosage of 20mg. This therapy is more effective than acetylcholinesterase inhibitors and has lesser side effects [25, 32].

Nowadays research proposes that a single therapy for multifactorial disease as AD has a low efficacy that invests them to go through poly-pharmacology which works on multiple targets; this includes either combination therapy (CT), multiple drugs working on different regions, or multi- target directed ligand (MTDL) where a single drug binds to multiple targets [33]. The fifth approved drug is a combination between memantine and donepezil, (Namzaric), that was approved by FDA in 2014 for treating individuals suffering moderate to severe AD. This combined therapy shows more effectiveness than single therapy by improving social and cognitive aspects. Nausea, vomiting, and diarrhea were the major digestive system related adverse effects [34].

2. Innovative Pharmacological Therapies

Small interfering RNA (siRNA) gene therapy is a promising approach for treating brain disorders such as Alzheimer's disease (AD), particularly by inhibiting Beta-Secretase 1 (BACE1), an enzyme crucial in the early stages of AD by initiating the production of toxic amyloid β (Aβ) [35, 36]. Research has shown that siRNA-based nanocomplexes can enter neuronal cytoplasm, reducing BACE1 mRNA expression by approximately 50%, which prevents synaptic damage caused by Aβ [24, 34]. In transgenic APP/PS1 mice, these nanoparticles not only promoted hippocampal neurogenesis but also inhibited amyloid plaque formation and tau protein accumulation, restoring cognitive function to levels seen in wild-type controls without significant adverse. effects on myelination [35]. Although developing non-peptidic BACE1 inhibitors with optimal pharmacokinetics and brain penetration has been challenging, inhibitors like MK-8931, LY2886721 (discontinued), and E2609 have shown mostly positive outcomes in clinical trials, including the EPOCH and APECS studies for MK-8931 [36]. Soluble Aβ oligomers are involved in the synaptic dysfunction associated with AD. They interfere with hippocampal long-term potentiation, disrupting spatial memory in rodents [40]. Many therapeutic attempts shifted their focus to neuroprotective agents to counter these neurotoxic intermediates, starting with growth factors. Promising

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molecules include basic fibroblast growth factor (bFGF), neurotrophins like nerve growth factor, glial-derived neurotrophic factor, brain- derived neurotrophic factor (BDNF), insulin-like growth factors (IGF-1/IGF-2), and bone morphogenetic proteins. For instance, PEG-PLGA nanoparticles loaded with bFGF have improved cognitive function in rats in the Morris test after exposure to β-amyloid and ionic acid [24, 34, 35]. AD alters levels of neurotrophic factors like BDNF, which regulates neurogenesis. Increased BDNF levels and neurogenesis have been observed in "Non-Demented with Alzheimer's Neuropathology" individuals, possibly contributing to preserved cognition, making BDNF a potential pharmacological treatment for AD [36]. Recent studies indicate that some antidiabetic drugs may offer neuroprotective effects in Alzheimer's disease. Gold nanoparticles have been shown to inhibit insulin fibril formation, delaying amyloid-like fibril development and demonstrating neuroprotection. Similarly, nanoparticles carrying the peptide NAPVSIPQ, with lactoferrin as a targeting ligand, improved cognitive function in mice by enhancing nose-to-brain delivery [35]. Additionally, supplementation with walnut peptides improved cognitive deficits and memory impairment in mice, while also restoring antioxidant enzyme levels and reducing inflammatory mediators at doses of 400 or 800 mg/kg. These results suggest that walnut peptides may protect against Alzheimer's disease by modulating inflammation and enhancing the antioxidant system [37]. The involvement of the NO cascade in memory mechanisms suggests that PDE5 inhibition could be useful in Alzheimer's therapy. Studies by Shim et al. found that chronic treatment with udenafil (100 mg) improved cognitive and executive functions in patients with erectile dysfunction, and a lower dose (50 mg) also enhanced cognition after 2 months. Both studies reported no severe adverse events or treatment discontinuations, indicating that long-term PDE5 inhibitor use may be necessary for cognitive benefits [38]. Moreover, drugs targeting the mitochondria and the inflammatory circuit are gaining increased recognition. For example, 3-n-Butylphthalide (NBP) may inhibit neuronal apoptosis by modulating the Akt/mTOR12 and GDNF/GFRAK1/Ret13 signaling pathways, with a recent clinical trial highlighting its protective effect on vascular cognitive impairment. Due to its multitargeted effects—such as reducing oxidative damage, improving mitochondrial function, and modulating mitochondrial dynamics—NBP shows promise as a potential pharmacotherapy for cognitive impairment, including that induced by brain microcirculatory disorders and mitochondrial dysfunction in Alzheimer's disease [39]. Recent studies suggest that regulating silent information regulator 1 (SIRT1) expression through natural molecules like resveratrol can provide significant neuroprotective effects and serve as a promising multi-mechanistic therapeutic strategy against Alzheimer's disease [40]. Notably, resveratrol nanocarriers have been shown to inhibit Aβ aggregation, reduce oxidative stress, suppress tau hyperphosphorylation, and improve memory impairment in AD mice, highlighting the need for further clinical trials to confirm their safety and efficacy in humans [35].

3. The Neurosurgical Approach in Treating Alzheimer's Disease:

Early and Current Neurosurgical Procedures

The quest to treat AD through neurosurgical interventions is a perpetually progressing and evolving journey which started from random highly invasive procedures which gradually evolved to more sophisticated procedures with high precision. As clearly pinned by the medical history, one of the first procedures proposed to manage AD was frontal lobotomy in the early 20th century. The book "Great and desperate cures: The rise and decline of psychosurgery and other radical treatments for mental illness" discusses that this surgery aims to disrupt the brain's prefrontal cortex circuitry intending to reduce the severe behavioral and psychiatric symptoms of severe and advanced dementia [41]. However, as the author Valenstein who highlighted the controversial nature of this procedure discussed, this procedure had a non-desirable outcome leading to personality changes and severe cognitive deficits and a high mortality and morbidity rate [41]. Following the decline of the invasive lobotomies, the focus shifted to less invasive techniques as cerebrospinal fluid (CSF) shunting. This technique was originally uploaded to practice to treat conditions live normal pressure hydrocephalus, however it was also explored in AD, and this was based on the proposed hypothesis that improving CSF circulation can help clear out the beta amyloid

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plaques which are pathognomonic for AD [42]. However, clinical practice has proven that this technique although is efficient in treating NPH, its efficacy in AD is inconsistent and is accompanied by several complications as subdural hematomas and shunt infections [42, 43]. As the neurobiology of the disease became clearer, the neurosurgical intervention shifted from ablative techniques to neuromodulation techniques. At the forefront of this shift was DBS targeting several brain areas particularly the fornix and other memory circuits. A pioneering study conducted elucidated the benefits of DBS targeting the fornix where patients showed some memory function improvements [44]. However, other advanced studies showed variable results where, in addition to cognitive improvements, some patients showed no benefits or worsened symptoms [45]. These mixed results underscore the essence of more research to refine both patient selection and stimulation parameters. Another explored neuromodulatory treatment for AD is Vagus Nerve Stimulation (VNS). This technique relies on the ability to enhance neuroplasticity and neurotransmitter release by the latter stimulation [46]. The study showed that VNS improved cognitive function in AD due to the increased release of norepinephrine involved in attention and memory [46]. Nonetheless, this evidence remains preliminary as other studies have shown mixed results [47]. In these studies, although some patients demonstrated cognitive improvements, others experienced side effects related to the function of the Vagus nerve as hoarseness, cough and even cardiac complications.

New Innovative Neurosurgical Procedures

Focused Ultrasound (FUS) is a very recent innovative technique that has opened avenues for treating AD. FUS transiently disrupts the blood brain barrier (BBB) which allows for therapeutic agents to reach the brain directly. Studies have shown the ability of FUS to reduce the amyloid plaque burden in animal models and early human trials where some patients showed cognitive improvements [48, 49]. However, the repetitive disruption of the BBB and its long term effects as well as the off-target effects remain areas of investigation. Another noninvasive technique is the cranial electromagnetic stimulation where it aims to modulate neuronal activity by inducing electric fields in specific brain regions associated with memory and cognition [50]. Evidence remains limited and most studies are small scale. Gene therapy is a more targeted approach. This technique aims to alter the expression of the genes implicated in the beta amyloid and tau pathologies [51]. The technique aims to either reduce the production of the beta amyloid or enhance its clearance [51]. Nonetheless the challenge of safely delivering the genes effectively to the brain as well as the concerns of long term safety have kept gene therapy in early experimental phases. Another promising area of research is stem cell therapy. Research highlights the potentials of this type of therapy to reverse the neurodegeneration seen in AD [52]. However, significant hurdles arise as risks of rejection, tumorigenesis and difficulty integrating the grafts into neural networks [52]. Tissue grafts and intraventricular infusions have been proposed to safely and efficiently deliver therapeutic agents to the brain directly bypassing the BBB and thus reducing the side effects [53]. These techniques on the other hand hold a risk of infection, inflammation and many other technical challenges. Finally, one of the most advanced areas of research to attenuate or treat AD is optogenetics. This approach is achieved by gene modulation so that neurons will express channels that are sensitive to light as channelrhodopsins [54]. When specific wavelengths of light are used, the channels will either open or close depending on its type and this leads to the alteration of the neuronal circuit [54]. The high precision of this technique opens a vast horizon for the advances in treatments of AD. However, this technique faces many technical and ethical issues so optogenetics in humans is still in its infancy.

Focused Ultrasound (FUS) and Intraventricular Infusions of Neuroprotective Factors in Alzheimer's Disease

Focused ultrasound (FUS) is a non-invasive approach that targets certain brain areas with high- intensity sound waves, thus breaching the blood-brain barrier (BBB) temporarily. This interruption enables improved delivery of therapeutic drugs that normally fail to pass the highly selective BBB [55]. When employed for treating Alzheimer's disease (AD), FUS turned out to be of good efficiency. FUS can cause a

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remarked decrease in amyloid plaques, which are pathologic hallmarks of Alzheimer's disease, by dramatically increasing the delivery of amyloid beta-targeting antibodies, as proved by research [56]. In addition, FUS intervenes with the delivery of neuroprotective factors directly into the brain through intraventricular infusions. This involves the administration of agents like brain-derived neurotrophic factor (BDNF) into the cerebrospinal fluid (CSF), allowing it to bypass the BBB. BDNF plays a crucial role in preserving neuronal survival and synaptic plasticity in learning and memory, both of which are impaired in AD, where AD is a disorder of the synapse [57, 58]. The safety and long-term efficacy of FUS in AD treatment are to be further ensured. While the technique shows promise, precise control over BBB disruption is necessary to avoid adverse effects, such as inflammation or tissue damage. To optimize FUS parameters and confirm its therapeutic potential in AD patients, further clinical trials should be done [59].

Cranial Electromagnetic Stimulation in Alzheimer's Disease

Cranial electromagnetic stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), were investigated for their ability to improve cognitive performance in Alzheimer's disease [60]. Transcranial magnetic stimulation (TMS) uses magnetic fields to generate electric currents in specific brain locations, mainly the dorsolateral prefrontal cortex (DLPFC). This area is important for cognitive functions including memory, attention, and executive function [61]. Cortical excitability and neuroplasticity are increased upon TMS application. Research showed that recurrent TMS (rTMS) enhances cognitive performance in individuals suffering from mild to severe Alzheimer's disease, notably in memory and executive skills [62]. TMS has a largely positive safety profile, with only modest side effects, including headaches and scalp pain [62]. In spite of these advantages, the cognitive benefits of TMS may be limited, and continuous interventions are usually necessary for maintenance [63]. More research is required to discover the appropriate stimulation settings and analyze the long-term effectiveness of TMS in AD patients [63]. Transcranial Direct Current Stimulation (tDCS) aims to enhance neuronal activity by changing the neuronal resting membrane potential. Such changes can be induced by placing scalp electrodes to apply a low-intensity electrical current [64]. tDCS may improve cognitive skills, including memory and attention, by focusing on particular brain areas [64]. This technique can boost cognitive function in AD patients, with noticeable enhancements in working memory and attention, as demonstrated by some meta-analyses [65]. The effectiveness of tDCS in Alzheimer's disease may differ among patients. While tDCS has a great safety profile with low side effects, cognitive advantages may vary depending on parameters such as electrode location and stimulation period [65]. The diversity of findings highlights the requirement for standardized protocols and more large-scale clinical trials to deeper comprehend the therapeutic potential of tDCS in AD [65].

Gene Therapy

Gene therapy, used in both non-inherited and inherited diseases, is the introduction of genes into patients' cells in attempt to add a new cellular function or to correct an existing genetic defect to restore function [66]. Gene therapy is done through delivering a viral vector mediated transgene; the virus infects the patient's cell and expresses its gene [67]. Gene therapy has been successfully used in a number of neurodegenerative genetic diseases and is now approved for some [67]. However, studies on gene therapy temporarily faced a safety obstacle related to the use of viral vector [67]. In AD, the potential and feasibility of gene therapy specifically in performing intracerebral gene delivery was studied and showed promising results [68]. The possible targets for gene therapy in Alzheimer's are the nerve growth factor, brain-derived neurotrophic factor, CD33, AD linked apolipoprotein E, and amyloid beta degrading enzymes [67]. Evaluation of efficacy and safety of this therapy in AD, specifically in the injection of DNA coding for the nerve growth factor that supports and enhances cholinergic neurons' function, was studied but did not show evidence for biomarker or clinical benefits [68]. Other than coding for NGF, the application of gene therapy in AD targets a transmembrane sialic acid binding receptor present on microglial cells' surfaces, Siglec-3 or CD33, causing its knockdown [69]. Interestingly, the knockdown of CD33 reduces

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neuroinflammation and amyloid beta accumulation which are the key contributors in the pathogenesis of AD [69]. Although utilizing gene therapy in the treatment of central nervous system (CNS) genetic diseases has led to significant therapeutic results, due to the multifactorial quality of Alzheimer's, applying gene therapy in a vast population of AD patients has been challenging not only for its safety but also for its appropriate target and accurate gene dosage [67]. Further promising research and ongoing clinical trials are needed to implement and approve safe efficient gene therapy for AD.

Stem Cell Therapy

Stem cells have the unique ability to differentiate into any cell [70]. Due to their high differentiation, proliferation, and self-renewal abilities, stem cell therapy has cast a new great potential and hope for the treatment of several diseases including the neurodegenerative disease, Alzheimer's [71, 72, 73]. Stem cell therapy is a new innovative revolutionary promising approach that utilizes the abilities of stem cells in differentiation in attempt to replace lost glial cells and neurons and restore endogenous neurogenesis, ultimately decreasing AD's pathogenesis [74, 75]. Stem cells sources of different properties include neural (NSC), mesenchymal (MSC), human embryonic (hESC), induced pluripotent (iPSC), directly induced neurons (iN), and olfactory ensheathing (OEC) stem cells [71, 72, 74, 76]. In recent years, stem cell technology advanced and has been proved successful in application to animal AD models as well as in recent preclinical AD studies [70, 72]. Animal studies proved that NSCs improve memory deficits when transplanted in the mouse AD model's hippocampus [74]. Other electrophysiological studies provided evidence on NSC's improvement of connections between synapsis [74]. Although stem cell therapy has a vast potential in overcoming the AD pathogenesis, research identified a set of drawbacks, challenges or limitations of this therapy's clinical application and medical surgical transition from the bench to bedside [70]. Research on different stem cell sources in relation to their AD application showed different results, advantages, and disadvantages according to the source type [71, 74]. Some stem cell sources' advantages include being easy to access, posing no ethical issues, having strong proliferation activity, having directional migration, and showing no histocompatibility [71, 74]. Disadvantages of some stem cell sources are strong immunogenicity, unclear mechanism of differentiation, proliferation, and migration, ethical issues, complex operation process, low efficiency, unrestrained differentiation, high risk for mutation, high risk for ejection reaction, and mostly tumorigenicity [71, 72, 74]. The disadvantages of some stem cells of different sources are to be thought of and considered in research for the clinical application of stem cell therapy in AD. This is to determine the best source for stem cell therapy in AD in accordance to research evidence. Future research work on stem cell therapy in AD needs to address technical considerations limiting its clinical application such as accurate dosing, long-term safety and efficacy, appropriate timing, required immunosuppression, preferred stem cell source, specific stem cell mode of action, precise delivery system, and potential side effects of stem cell therapy application in AD all of which are still indetermined by research [70, 73]. Researchers should put in immense effort to translate and transfer results of animal and preclinical studies to human clinical trials to pave the path for an innovative, individualized, effective, and most importantly, safe treatment for AD patients.

Optogenetics

Optogenetics is a blend of optics and genetic engineering that uses specific wavelengths light to activate or inhibit specific cells [77, 78]. Optogenetics has shown promise in a number of disorders and diseases, mainly Parkinson's and epilepsy [78]. Very few studies have been published about the topic of optogenetics application in AD [78]. Optogenetics is a new innovative cutting-edge technique that is now being researched for its implementation in AD, its safety and efficacy in AD [79]. Optogenetics in AD is used to restore neural functions and precise circuits that are disrupted or destroyed by Alzheimer's through selectively activating specific neurons involved in learning and memory. The potential of optogenetics in AD lies in its selective and precise neural inhibition or activation to mitigate cognitive deficits and counteract AD's impact [79]. On the other hand, there is a list of obstacles to the application of optogenetics

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in AD in a clinical setting. One obstacle is the complex invasive delivery of optogenetics constructs to brain regions targeted. In addition, optogenetics require specialized professionals in the technicalities of optogenetics [79]. In a study on a mouse model, optogenetic gamma stimulation rescued memory limitations [80]. In other animal studies, optogenetics regulated connectivity between synapsis and improved memory function [77, 78]. Research on the safety, efficacy, and therapeutic potential of optogenetics in AD is needed to translate results from animal to human models in clinical trials, to potentially treat AD. Optogenetics is an innovative fascinating approach to AD pathogenesis; it holds promise and notable potential for future AD treatment.

4. Comparative Analysis and Evaluation of the Treatment options

The comparative evaluation of pharmacotherapy and the neurosurgery in the treatment of AD is complex given the novelty of the latter and the recent emergence of innovative techniques in both approaches being in the early stages of preclinical testing.

Effectiveness and Safety of Early Treatment Options

While Tacrine has shown to cause hepatotoxicity, early neurosurgical procedures as frontal lobotomy had severe and abusive side-effects, a stage that has called for further research and advancement for better and safer treatment options.

Effectiveness and Safety of Current Therapies

According to the above highlighted evidence, both Ach esterase inhibitors, namely Memantine and the combination therapy, and the neurosurgical procedures (DBS and VNS) have shown promise in treating Alzheimer's Disease by being sufficiently effective in alleviating the symptoms, restoring cognitive function to a certain extent and having limited and manageable side-effects. However, while the drugs have been widely used by the target population, the neurosurgical procedures have shown mixed results. Also, while the drugs have resulted in minor gastrointestinal side-effects, the surgical procedures yielded major cardiac complications. This analysis suggests that current drugs still hold as a safer treatment option taken into consideration the comparable effectiveness.

Effectiveness and Safety of the Innovative Treatment Options

Innovative pharmacotherapy involves the introduction of nano-complexes, nano-particles, neuroprotective or neurotrophic factors that counter the stress and damage caused by the accumulations. Interestingly, some of these are found in natural substances as walnut peptides and resveratrol guaranteeing safety. In addition, it holds great effectiveness in promoting cognitive health and memory proven by the several clinical trials done. On the other hand, innovative neurosurgical procedures display huge success and promising role in restoring cognitive performance but are unfortunately still being tested for safety with calls for more validating clinical trials. This is because many techniques are still in the preclinical stage and are limited by a number of obstacles, including BBB integrity, invasiveness, genetic heterogeneity and dosage formulation in addition to ethical approval. This is not to underestimate the importance of developing and advancing such techniques especially that one of them, tDCS, has shown high safety and good effectiveness with a little attention and research needed for personalizing the location and duration of the stimulation. Hence, it appears that pharmacotherapy is a more valid treatment option for the time being according to the criteria of safety and effectiveness. This analysis done reveals the need to put huger effort in conducting more clinical trials for AD innovative treatment options since neither option has yet succeeded in slowing or preventing neurodegeneration.

Evaluating pharmacotherapy and neurosurgery in the context of life quality and cost- effectiveness

Quality of Life

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Recent studies show that Ach esterase inhibitors are the optimal medication for people suffering from mild to moderate AD, improving their cognition abilities, global performance and feasibility of daily life activities [81]. Out of the practiced neurosurgical treatments, DBS has shown strong promise in improving the patients' quality of life [82]. As for the other emerging neurosurgeries, none has ever performed on humans, so it is not applicable to evaluate them based on this criterion.

Cost-effectiveness

Concerning acetylcholine esterase inhibitors, recent studies demonstrate the disparity in the availability of such drugs by race and ethnicity which some-how clarifies the economic burden of utilization by some groups. To elucidate, in the American community, these drugs are available among whites more than non-whites. Also, out of all patients, only 40% initiate the treatment within the first 6 months after symptoms diagnosis [83]. Among the Ach esterase inhibitors, donepezil appears to be the mostly-cost effective option in people with mild-moderate AD; galantamine is slightly cheaper but with lower effectiveness. However, evaluating the mostly cost-effective drug remains controversial given the continuous changes in effectiveness and costs [84]. However, it is always recommended to go for early diagnosis and treatment to manage and decrease the health and social care costs as demonstrated by a recent Finnish study [85]. On the other hand, concerning the few applied neurosurgical procedures, of which is DBS, research suggests examining specific thresholds and success rates to decide whether performing DBS is more efficient and cost-effective in the long run than the standard treatments; so the matter differs case-wise [86]. As for the other innovative neurosurgical procedures, including stem cell therapy and gene therapy, studies display the cost hurdle in conducting clinical trials and translating the results. It is estimated that maximum cost-effective price for gene therapy is 141,126 $ per treatment at threshold, this price doubles if we increase the effectiveness to 50% based on Markov simulation analysis [87,88].

Conclusion

Alzheimer's disease has been a critical, increasingly spreading health dilemma putting a huge social burden on the healthcare providers in addition to an immense economic burden on the healthcare systems. This has necessitated a great effort to search and advance the available treatment options in an attempt to get the optimal therapy. Despite the continuous advancements in pharmacotherapy and recently in neurosurgery, no curative treatment has been found yet and the controversy of evaluating the better available choice of treatment still holds. However, while innovative neurosurgery paves a way for semi-curative treatment, pharmacotherapy is still the safer, affordable and accepted as an effective option. Current research focuses on building new perspectives in targeting Alzheimer and in the synthesis of new drugs. Moreover, successful pilot studies recommend seriously taking precision medicine as an approach to treating Alzheimer's disease.

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Author Contributions

Mariam Moselmani: conceptualization, data collection, writing original draft. **Monifa Al Akoum:** writing original draft. **Rita Haddad:** writing original draft and reviewing. **Fatima Mortada:** writing original draft. **Ahmad Atieh:** writing original draft and reviewing. **Hiba Malaeb:** writing original draft. **Zeinab Jabak:** writing original draft. **Aya Kawssan:** conceptualization, editing, writing original draft and reviewing.

Conflict of interest

The authors declare no conflict of interest.

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