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A Review of Existing and Emerging Treatment Interventions for Alzheimer's Disease

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Abstract

Cognitive decline and progressive neuropathy due to Alzheimer's disease (AD) are on the rise throughout the world today. By impairing function and reducing the affected person's quality of life, it worsens the global burden of the disease. Many treatment options are available; however, it is important to note that each has its pros and cons and should be compared side by side to develop an individualized therapeutic approach. While a few new advanced therapeutic discoveries gain traction, such as the use of polyethylene glycol (PEG)-modified black phosphorus nanosheets (BP-PEG) and revolutionary gene editing using CRISPR/Cas9, there is a need for more data available from clinical trials for a better understanding of the new techniques being worked on. Some advancements, although promising, have yet to progress from animal models to human clinical trials. A call for further investigation appears to be necessary to weigh the advantages and disadvantages of both pharmacological and non-pharmacological therapy for AD.

Keywords: Alzheimer disease; Cognitive dysfunction; Therapeutics; Pharmacology

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Introduction

Alzheimer's disease (AD) is a progressive neurological condition marked by cognitive decline and memory loss. This review explores diverse treatment strategies, including cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and memantine, which have demonstrated efficacy in managing AD symptoms. Targeted therapies aimed at removing amyloid plaques through antibodies, as well as enzymatic and non-enzymatic mechanisms, have shown promise in modifying the disease course. Additionally, strategies targeting tau protein misfolding and aggregation, such as tau modification enzymes and protein clearance pathways, aim to slow disease progression. Recent research indicates that phosphorylated tau (P-Tau) can be cleared from the brain into the bloodstream, and polyethylene glycol (PEG)-modified black phosphorus nanosheets (BP-PEG) are a promising treatment avenue. Anti-inflammatory treatments may also reduce inflammation and restore neuronal function in AD patients. Family care and cognitive therapy are recognized as valuable therapeutic approaches.

Furthermore, the revolutionary genome-editing technique, CRISPR/Cas9, holds significant promise for diseases like AD, which have limited treatment options. Advances in animal model studies with stem cells offer encouraging outcomes for potential novel AD treatments. Electrical neural stimulation, particularly deep-brain stimulation (DBS), also shows potential for alleviating memory loss in some AD patients. Non-invasive techniques such as gamma-band neural stimulation and radioelectric asymmetric brain stimulation (REAC) present alternative options for individuals unresponsive to traditional treatments. Additionally, focused ultrasound with microbubbles (FUS-MB) holds promise as a non-pharmacological method to enhance drug delivery for AD treatment by opening the blood-brain barrier. In this article, we aim to provide a brief overview of the aforementioned therapeutics and their known efficacy thus far. By doing so, we hope to provide a snapshot of the various techniques under development to tackle this degenerative neurological condition.

Pharmacological Treatment

Cholinesterase Inhibitors

In Alzheimer's disease, acetylcholinesterase activity increases, depleting the neurotransmitter acetylcholine, which is required for optimal brain function.[1] Cholinesterase inhibitors, such as donepezil, galantamine, rivastigmine, and memantine, are used, which have an effective role in enhancing cognitive function in people with Alzheimer's

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disease.[2]

Cholinesterase inhibitors work by blocking the action of acetylcholinesterase, which breaks down acetylcholine.[1]

Symptoms of Alzheimer's disease can be managed with Donepezil, a second-generation acetylcholinesterase (AChE) inhibitor.[3] In vitro findings show that donepezil is a reversible, mixed competitive and noncompetitive AChE inhibitor.[3] However, adverse effects can occur during utilization, and they are more common at larger dosages.[4] These include appetite loss, vomiting, nausea, diarrhea, and rhinitis with gastrointestinal side effects.[4]

Rivastigmine is another reversible cholinesterase inhibitor that targets both acetylcholinesterase and butyrylcholinesterase, another enzyme that breaks down acetylcholine.[5] It is classified as a pseudo-irreversible inhibitor since it binds to AChE, which cleaves the rivastigmine molecule.[6] As a result, a covalent carbamoyl-AChE complex is produced, blocking acetylcholine catalysis and temporarily inactivating the enzyme.[6] Initially, rivastigmine was administered orally; however, given its unfavorable gastrointestinal symptoms, a transdermal patch was developed. This allowed for continuous, regulated drug administration while preventing changes in plasma levels.[7]

Galantamine is a reversible competitive and selective inhibitor of AChE that interacts with the anionic subsite and the aromatic gorge of AChE.[8] It upregulates the nicotinic receptors.[8] Galantamine improves cognitive function and is used in treating mild to severe Alzheimer's disease.[9] The adverse effects of this medication resemble those of other acetylcholinesterase inhibitors, primarily manifesting as gastrointestinal symptoms. Galantamine appears to be less tolerated in comparison to other drugs used in Alzheimer's disease treatment.[8]

Memantine is an anti-Alzheimer drug that works as an NMDA (N-methyl-D-aspartate) receptor antagonist.[10] It is known that excessive NMDA receptor activity, due to tau aggregates, fills the dendrites with toxic amounts of calcium.[11] Excitotoxicity caused by calcium can harm postsynaptic regions, resulting in neuronal death.[11] Memantine, a next-generation NMDA antagonist with its well-tolerable profile at clinical doses, has been approved for treating moderate to severe Alzheimer's disease.[12]

Amyloid Plaque Removal

The development of amyloid plaque removal therapies is an important field of study in the hunt for effective Alzheimer's disease treatments. Amyloid plaques are aberrant protein aggregates made up mostly of amyloid-beta that are suspected to play a role in the genesis and progression of Alzheimer's disease.[13] Amyloid plaque accumulation causes neurotoxicity and contributes to the production of neurofibrillary tangles, another characteristic of Alzheimer's pathogenesis.[13] Amyloid plaque removal therapy in Alzheimer's disease refers to experimental treatments targeted at lowering or eliminating amyloid plaque deposition in the brain.[14] This has the potential to delay the course of the disease and improve cognitive function by lowering the load of toxic amyloid aggregates.[13] Some interventions involve using antibodies or vaccinations to target and remove amyloid-beta from the brain.[15] These aim to boost the body's immunological response to amyloid plaques, making them easier to remove. Monoclonal antibodies such as aducanumab have shown promise in some clinical trials among these treatments.[15] More recently, scientists are investigating the use of enzymatic and non-enzymatic mechanisms that can degrade amyloid-beta proteins, facilitating plaque clearance.[16]

Tau Protein Pathology and Removal

Tau protein is another crucial factor in Alzheimer's pathology.[17] In healthy neurons, tau stabilizes microtubules that maintain cell structure, and it also plays an important role in protecting DNA and RNA.[18] Physiologically, tau is a soluble and unfolded protein; however, under pathological conditions, it becomes insoluble and aggregates form paired helical filaments and neurofibrillary tangles.[18] Tau needs to be phosphorylated at specific sites to function normally; however, improper phosphorylation or hyperphosphorylation causes it to convert to a pathogenic form.[18] There are many approaches for slowing down the rate of neurofibrillary degeneration.[19] These involve blocking tau-modifying enzymes like glycogen synthase kinase-3β and cyclin-dependent protein kinase 5.[19] Other strategies involve activating a key tau protein regulator called protein phosphatase-2A, enhancing tau protein modification by β-N-acetyl-glucosamine.[19] This is accomplished by inhibiting β-N-acetylglucosaminidase.[19] Lastly, improving the brain's absorption of glucose can aid in the ubiquitin proteasome system or autophagy process to eliminate tau proteins that are hyperphosphorylated.[19]

Recent research has shown that phosphorylated tau (P-Tau) can cross the blood-brain barrier and enter the peripheral circulation.[20] This discovery suggests that organisms have a mechanism to clear P-Tau through organs like the liver and kidneys, which can potentially reduce P-Tau levels in the brain.[20] Utilizing this peripheral pathway for P-Tau clearance offers a promising and safe approach for Alzheimer's disease treatment, avoiding the challenges of the blood-brain barrier.[21] In one interesting

study, scientists developed polyethylene glycol (PEG)-modified black phosphorus nanosheets (BP-PEG), which circulated in the body for long periods of time, efficiently eliminating peripheral P-Tau, functioning as effective "garbage trucks".[21]

Anti-inflammatory Strategies

Neuroinflammation is believed to play a role in Alzheimer's disease progression, making it a promising target for treatment.[22] Inhibiting inflammation can restore neuronal function, promote neuroregeneration, and reduce the disease burden, potentially improving or even reversing symptoms.[23] In addition to examining the connection between inflammation and Alzheimer's disease hypotheses, this review also explores different pharmacological categories such as small molecules (e.g., nonsteroidal anti-inflammatory drugs), macromolecules (e.g., peptides, proteins), and nanocarriers (e.g., lipid-based nanoparticles).[23] The use of nanocarriers to develop anti-inflammatory techniques for the treatment of Alzheimer's disease is recommended.[23]

Non-pharmacological Treatment

Family care

A structured interview study explored attitudes towards non-pharmacological interventions in dementia care, involving health professionals, family caregivers, and individuals with dementia.[24] The focus was on understanding family caregivers' experiences, obstacles, and views on the effectiveness, suitability, and financial aspects of these interventions.[24] Two caregiver categories were studied: spouses providing home care and relatives offering care outside the home.[24] The study's conclusions imply that family caregivers who observe improvements in dementia symptoms often employ non-pharmacological therapies.[24] In particular, social contact is thought to improve well-being, prevent orientation problems, postpone cognitive deterioration, and aid in depression.[24] Nonpharmacologic intervention deployment, however, is contingent upon organizational effort, money, local availability, and the intervention's apparent efficacy.[24] Thus, counseling for individuals with dementia and their family caregivers should include both education about non-pharmacological strategies in dementia care, and assistance in implementing them.[24]

Cognitive therapy

Cognitive therapy is becoming more popular alongside drug-based therapies for Alzheimer's disease. A 2019 analysis examined data from 33 cognitive treatment trials from 12 countries.[25] It was concluded that cognitive training, such as guided practice on structured tasks, is likely associated with small to moderate improvements in general cognitive function and language ability.[25] Furthermore, in individuals with moderate Alzheimer's disease, cognitive stimulation has been shown to improve memory, attention, and executive functioning successfully; however, at the 3-month follow-up, these benefits start to fade.[26]

Gene Therapy

Gene editing and gene silencing techniques hold promise for novel treatment approaches.

CRISPR/Cas9 is a recently discovered and promising breakthrough method for genome editing that enables the treatment of diseases with limited therapeutic options.[27] Even though undesirable mutations constitute just under 1% of Alzheimer's disease cases, with the rest of the cases being sporadic, these mutations result in increased production of Aβ.[28] Genome editing with CRISPR/Cas9 for autosomal dominant mutations in genes such as presenilin 1 (PSEN1) and presenilin 2 (PSEN2) may be beneficial in familial Alzheimer's disease.[27] However, this technique would provide low or negligible advantages in sporadic Alzheimer's disease, which involves unidentified triggers.[27]

Stem Cell Therapy

Stem cell therapy is a key focus in neurological disease research, particularly for Alzheimer's treatment.[29] Studies suggest that neural stem cells can develop into functional neurons, potentially replacing damaged ones and forming connections with existing neurons. This process may help restore neuronal connections and reduce neuroinflammation.[29] The four major types of stem cells used in Alzheimer's disease therapy (neural stem cells, mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells) have shown applicability not only in cellular levels of treatment or in animal models, but also in clinical settings.[29]

Recently, the transplantation of neural stem cells (NSCs) has emerged as a potential therapy.[30] By releasing chemicals that prevent Alzheimer's disease (AD) symptoms from further deteriorating, and changing the level of proteins in damaged areas, these transplanted cells have the potential to restore damaged brain circuitry.[30] However, it is difficult to accurately characterize the positive outcomes of transplanting NSCs because there are animal models that can replicate all aspects of Alzheimer's disease.[30] A review examining the effects of transplanting human-derived NSCs (hNSCs) or murine-derived NSCs (mNSCs) on mouse models, along with other NSC transplantation studies, suggests that this method may prove to be a useful therapeutic strategy for Alzheimer's disease.[30]

Impaired neuroplasticity, exacerbated by aging and

cognitive decline, is a key sign of early Alzheimer's disease.[31] Detecting these deficits early could significantly enhance AD diagnosis and intervention.[31] Neural stem cells (NSCs) offer several advantages, including self-renewal, versatile differentiation, low risk of immune rejection, the ability to regulate the immune system, and the release of molecules that promote neuroplasticity.[31] NSC transplantation has been shown to address AD-related neuronal and synaptic loss in mouse models by activating the brain-derived neurotrophic factor (BDNF) pathway to promote neuronal survival.[31] Furthermore, NSCs also mitigate neuroinflammation and aggregation of amyloid-beta and tau proteins.[31] Their clinical use holds potential as a safe and effective AD treatment.[31] Therefore, leveraging NSCs to regulate neuroplasticity offers a promising approach for AD regenerative therapy, given the advancement into clinical trials from pre-clinical trials, and further investigation into an optimal therapeutic window for the treatment.[31]

Electrical Neural Stimulation

Among various categories for neurosurgical treatment for Alzheimer's disease, other than gene therapy, electrical neural stimulation appears to show results that warrant attention in mild to moderate Alzheimer's disease.[32] Deep brain stimulation (DBS) needs additional research before being used in a clinical setting; however, it appears to stabilize or reduce the rate of memory loss in some Alzheimer's patients in preliminary clinical studies.[33] Improved long-term potentiation, increased hippocampal neurogenesis, neuroprotection through neurotrophic factor release, diffuse reactivation of hypoactive neocortical associative areas, and restoration of hippocampal theta rhythms are some of the possible mechanisms through which DBS is expected to work.[33] Before implementing DBS in the clinical setting, however, some factors need to be addressed and require further research.[33] These include identification of the best candidates for the treatment, symptoms to be targeted, appropriate region to target for DBS, deciding on the type of stimulation modality to be used (continuous, intermittent, theta-bursts, or closed-loop stimulation), along with consideration of ethical concerns for the treatment.[33]

There are certain non-invasive brain stimulation techniques as well for the treatment of Alzheimer's disease. Among these, gamma-band neural stimulation may be ideal for AD prevention and treatment.[34] Although this is a relatively new area of research, this method of using gamma frequency to modulate neuronal activity shows sufficient evidence to support widespread adoption.[34] Additionally, radioelectric asymmetric brain stimulation (REAC) may be a suitable alternative for patients who do not respond well to pharmacological treatment for Alzheimer's disease.[35] This treatment has been shown to improve behavioral and psychiatric symptoms of dementia (BPSD) in elderly patients with AD.[35]

Combination Therapy

Lastly, an example of non-pharmacological therapy aiding the implementation of pharmacological therapy is focused ultrasound (FUS).[36] Studies on animal models showed that FUS with microbubbles (FUS-MB) generated an opening in the blood-brain barrier (BBB).[36] It is speculated that this might make it easier for pharmacological treatment to enter the brain.[36] These studies also showed frequent stimulation with both FUS-MB and FUS to enhance memory and cognitive performance.[36] More importantly, FUS stimulation has also shown improvement in local perfusion and neuronal function in human studies, which implies improved cognition.[36] Repeated FUS-MB is also well tolerated, with few adverse effects, encouraging its clinical implementation.[36] Regardless of its safety and practicality, this drug delivery approach requires further enhancement before being approved for widespread clinical use for the treatment of Alzheimer's disease.[36].

Conclusion

Alzheimer’s disease remains one of the most challenging neurodegenerative disorders with no definitive cure yet. Current pharmacological treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, offer only symptomatic relief. Novel strategies, including amyloid and tau-targeted therapies, gene editing, and stem cell transplantation, show promising potential to modify disease progression. Non-pharmacological approaches like cognitive therapy, family care, and neural stimulation further enhance patients’ quality of life. The combination of pharmacologic and non-pharmacologic methods, supported by technological innovations such as focused ultrasound, represents a comprehensive treatment direction. However, most emerging therapies still require validation through robust human clinical trials. Continued interdisciplinary research is essential to translate these experimental findings into effective, accessible treatments for Alzheimer’s disease.

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Ethical Consideration
None.

Competing Interests
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