Review, analyses, and comparisons of interventions in active and completed clinical trials of Alzheimer's disease

Aaryan Shah[1]

[1] Irvington High School, 41800 Blacow Road, Fremont, California, United States of America, 94538

Abstract

Alzheimer's disease is an incurable neurodegenerative disorder causing deteriorating cognitive function and memory loss. The purpose of this paper is to create a comparable landscape of completed and current clinical trials and therapeutic interventions for Alzheimer's disease, identifying future hallmarks of neurodegenerative research. In the status quo, the urgency for new drugs and interventions surges as the aging population and cases of cognitive impairment grow. Current FDA-approved drugs have only decreased disease progression slightly; these drugs last for brief periods and are useful for symptom management rather than reversing pathogenesis. Through the data compilation, intervention analysis, and the corresponding figures that provide a visual perspective of the respective trends, this review article effectively identifies the developments and gaps for intervention in Alzheimer's disease clinical trials. The methodology follows the specific guidelines and reporting standards of the Methodological Expectations for Cochrane Intervention Reviews (MECIR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Moreover, inclusion and exclusion criteria were centered upon publication date, trial results, and a multitude of keyword searches pertaining to Alzheimer's disease and cognitive impairment. Based on the review of clinical trials and literature precedent, descriptions of advancements are provided. Examples of these developments include the new interventions of stem cell therapy and declining trend of active immunotherapeutics. Trial details about the specific interventions were compiled using the ClinicalTrials.Gov database. Analysis of pending and completed trials are discussed based on advancements in Alzheimer's disease research and the progression of drug development.

Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that causes neuron degeneration, synaptic dysfunction, and cognitive impairment. As life expectancy and the aging population grow, the percentage of the aging community with cognitive dysfunction and impairment consequently rises. The World Alzheimer Report asserts that by 2050, the number of people affected will triple to approximately 152 million people, while the economic cost will double to two trillion dollars by 2030.[1] Expenditures for AD continue to rise (alongside worsening symptoms and rising mortality rates) due to pharmaceutical needs for aging symptoms, caregiver burdens, insurance premiums, and high out-of-pocket costs.[2,3] Even with the abundant research currently conducted, the Food and Drug Administration (FDA) has yet to approve a drug since 2003. Clinical trials have empirically failed due to limited recruitment that can be attributed to concerns of invasive procedures, exclusion criteria for underrepresented minorities, and lack of caregivers and study partners able to track daily functioning.[4] Many trials reaching Phases 2 and 3 status have had poor results for patients with dementia, some of which are discussed in subsequent sections. The four FDA-approved drugs (donepezil, memantine, rivastigmine, and galantamine) failed to show positive results for reversing pathogenesis and have only slowed symptoms for patients.[5] Each of these drugs has presented treatment-emergent symptoms, and branded drug Namzaric, a combinatory therapy of donepezil and memantine, reported adverse clinical symptoms such as seizures, ulcers, and muscle spasms.[5] 2011 guidelines of the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework conclude that AD is normatively defined by the pathological processes that can be documented by biomarkers or post-mortem examination.[79] This focus on biomarkers posits two major protein deposits seen as major markers of AD: amyloid-beta (Aβ) and phosphorylated tau. These abnormal protein deposits are key to understanding AD as these protein deposits, while not necessarily causal, are the unique, defining marker of AD that differentiates it from other neurodegenerative disorders.

Corresponding Author:
Aaryan Shah
shahaar13@gmail.com

The amyloid hypothesis proposes that the amyloidogenic cascade that leads to abnormal Aβ deposition begins with the improper cleavage of the amyloid precursor protein (APP). Secretases cleave APP in an amyloidogenic pathway, producing Aβ protein-peptide fragments that aggregate as neuritic plaques; major biomarkers of cognitive impairment and AD. This dysregulation produces 42-amino acid chain peptides, better known as Aβ-42. Additionally, Aβ-42 has been hypothesized as the cause of neurofibrillary tangles (NFT) composed of tau.[6] This hypothesis proposes that Aβ-42 is a precursor to plaque deposition in the brain along with NFT linked to AD pathogenesis, as concluded by the NIA-AA framework results. However, after 20 years of support, failing clinical trials and therapies question the amyloid hypothesis. Post-mortem reviews of patients with dementia noted that the linkage between tau-based NFTs and AD pathogenesis was stronger in relation to amyloidogenic plaques, along with evidence of NFT formation without plaque deposition; potentially representing independent relations of tau and cognitive impairment.[7,8] The tau hypothesis, in recent trials, seems more relevant in the progression of cognitive impairment presented in patients with AD. The hyperphosphorylation of tau protein causes microtubule disassembly, leading to NFT aggregation and neuron degeneration. The NFT formation blocks synaptic function and causes cell death; one proposed mechanism of cognitive dysfunction.[9] Investigations of the tau hypothesis present it as a prime focus for future drug development. Additionally, experts agree that AD drug development should move beyond mainstream hypotheses like tau and amyloid.[10] Many of these hypotheses work in conjunction with pending research based on literature precedent. Microglia-mediated phagocytosis successfully cleared amyloidogenic plaques, supporting evidence of microglial inflammation as a potential cause of AD. Additional evidence explains that glial cells are more abundant near plaques and NFTs.[11] Dysfunctional bio-metal homeostasis presents strong linkage to plaques and NFTs in patients with AD.[12] The cholinergic system hypothesis (acetylcholine degradation) is the theory with the most successful trials; donepezil, galantamine, and rivastigmine are cholinesterase inhibitors.[5] Elevated calcium levels with astrocytic inflammation are proposed as a biomarker of AD pathogenesis; memantine is a FDA-approved drug focused on calcium homeostasis and regulation.[13,14] The myriad of listed hypotheses have made investigational interventions critical in understanding AD and cognitive impairment. The 2011 NIA-AA framework encourages focus on the biomarkers through the lens of these hypotheses; essentially, rather than associating the potential hypotheses to the displayed clinical symptoms, the hypothesized pathways should be associated with the primary biomarkers of Aβ and abnormal tau.

Due to this framework, neuroimaging and biomarker tracing remain a major research focal point, as researchers attempt to find ways to diagnose patients before reversing pathogenesis. Past trials indicate that multiple imaging studies classified as "Procedural intervention" use technology, such as positron emission tomography imaging (PET).[15-17] PET focuses on in vivo structural imaging in preclinical studies and can identify NFT accumulation.[18,19] Other procedural interventions and imaging studies are discussed in the *Results* section.

This review report discusses the differences between active and completed trials while identifying gaps within the current development pipeline. This interventional review exemplifies the current differences in clinical trials and the potential pipelines for drug development, symptom management, and other ways to mitigate the main biomarkers seen in AD. Additionally, novel therapies are discussed based on ClinicalTrials.Gov data, classified based on the type of intervention. Details regarding the selection of overarching categories are described in the Methods section.

Objectives

The primary objectives of this review article are to improve systematic understanding of AD research through the lens of clinical trial registry review.

1. Through interventional analysis, the differences in pending and active trials can support new scientists and clinicians in identifying potential therapies, novel solutions, and cross-applicable molecules (e.g. using medications for other disorders).
2. Using this information supports cross-collaboration by researchers interested in studying similar therapeutic methods, leading to improved standardization of protocols; protocol standardization alleviates issues with study design differences and result comparisons.

Methods

Search strategies

The holistic review process of clinical trials began in May 2020. Using the "Advanced Search" tool on ClinicalTrials.Gov, restrictions were applied regarding dates, status, keyword searches, and additional details described in the various exclusion and inclusion criteria below. The World Health Organization's International Clinical Trial Registry Platform (ICTRP) was initially planned to be used, but has been temporarily unavailable due to heavy traffic caused by the COVID-19 pandemic; ICTRP is a future direction that researchers may consider to analyze results in this study. Due to the specific consideration of clinical trials, only trial registries were utilized to find information; the benefits from research conducted on other registry platforms other than ClinicalTrials.Gov were minimal. The distinct requirements between clinical trials registries could lead to major disadvantages in trying to analyze the trends for the clinical trials listed. Examples include the search interfaces for major registries, including ClinicalTrials.Gov and ICTRP, which could lead to different search results using the same key terms.[76] As ClinicalTrials.Gov is the most expansive registry offered, a focus on one specific registry was essential to support the accuracy of an interventional review in a specific clinical trials registry. Including multiple registries would have complicated the analysis and caused further discrepancies due to differences in reporting standards, search interfaces, and other registry-specific information. The search protocol was based on guidelines and strategies described in the Methodological Expectations for Cochrane Intervention Reviews (MECIR) Manual created by the Cochrane Library.20 The following paragraph describes the specific protocols and criterions applied to the systematic registry review.

Date restrictions were applied from 2005 onward, as the International Committee of Medical Journal Editors (ICMJE) ruled that clinical trials must be cited in public trial registries before

publication opportunities in July 2005.[21] The following keywords were utilized in searches in the "Conditions or Disease" search bar on the ClinicalTrials.Gov database: "Alzheimer Disease", "Alzheimer Disease, Early Onset", "Alzheimer Disease, Late Onset", "senile dementia", "cognitive impairment", "cognitive decline", "cognitive dysfunction", "cognitive deterioration", "Dementia", "Dementia Alzheimers", and "Dementia of Alzheimer Type". AND/OR operators were not available while searching in the clinical trial registry, thus justifying the wide keyword search. In order to separate active and completed trials, status filters were chosen while searching for trials ("Active, not recruiting" trials represented active trials with pending results and "Completed" trials represented completed trials since July 2005). Figure 1 describes the screening and selection process for clinical trials after the initial search. Phase I included the initial search on the ClinicalTrials.Gov database, along with the removal of duplicate studies or separate data entries for existing trials. Phase II incorporated the various exclusion and inclusion criteria, and Phase III finalized trials along with the data extraction, categorization, and appraisal processes.

Inclusion Criteria

Clinical trials were included based on dates (starting July 2005 to May 2020, the time of the screening process) and limited to trials published in English. No criteria were applied to the specific locations of the trials to access as much reliable information from across the globe. The use of a United States-centric trial registry could possibly exclude trials from other regions unintentionally due to language and cultural barriers.

Exclusion Criteria

All observational studies were excluded during the screening process to investigate specific interventions associated with the purpose of the study. Studies published prior to July 2005 were excluded. For the search of completed trials, trials were required to have detailed, reported results to determine the reliability, accuracy, and quality of the provided information about investigational trials.

Data Extraction

The following information was extracted per trial: the full title, location, study design, interventions, outcomes, and website hyperlink. All data was checked for errors in characterization of intervention and outcome measures. Further information regarding standardization is provided in the Categorical definitions subsection and describes how various therapies were categorized based on the type of intervention used in each study. Figure 2 was created based on the data extraction and categorization processes in Phase III (Figure 1).

Critical Appraisal

Critical appraisals are essential for determining accuracy and relevance of results and analysis during systematic reviews and other research methods. In this study, the Critical Appraisal Skills Programme (CASP) checklist tool was used to ensure the quality of each trial. The checklist was adopted based on the CASP randomized clinical trial checklist rather than the systematic review checklist to specifically cater towards the purpose of this study.[22] The study used a modified version of the CASP trial checklist to consider sample size, sample demographics, thoroughness of the trial, and reported results. Each study was ranked on a scale for assessment accuracy and bias, based on numerical assignment; another modification from the original checklist released by CASP. As mentioned previously, each completed trial was required to have detailed outcome measures as well as results, which could additionally be classified under the critical appraisal for each trial. Through all the appraisal steps in Phase III, the list of trials was finalized. Information regarding the search results is described in the *Results* section below. This search protocol has not been pre-registered due to the ongoing prioritization of COVID-19 and public health-related review protocols.

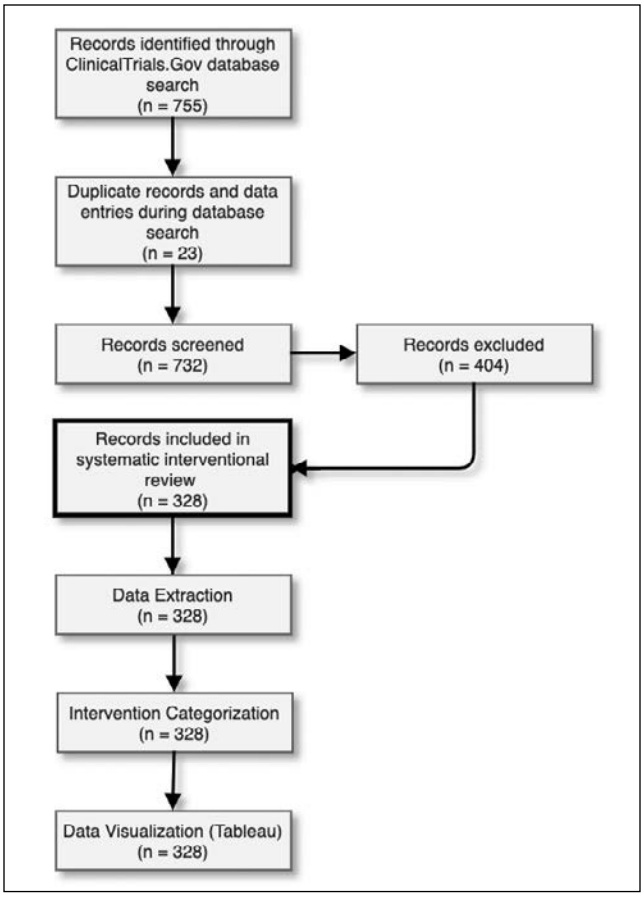

Figure 1. Screening flow diagram based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 328 active and completed trials were analyzed

Results

Search Results

The main focus of this review article is the comparisons and analysis of interventions, relevant details, and gaps and developments in AD clinical trials. The screening process was adapted from the PRISMA selection process (Figure 1).[23] 220 completed trials with reported results and 108 active trials pending results meeting the requirements of the criteria and critical appraisals were chosen for review as of May 28, 2020. Trials added subsequently were not considered. Various intervention-outcome combinations in clinical trials isolated by status (active or completed) were also analyzed (Table 1). Table

Table 1. Systematic compilation of intervention-outcome relationships in current and past clinical trials and therapeutic interventions in Alzheimer's disease

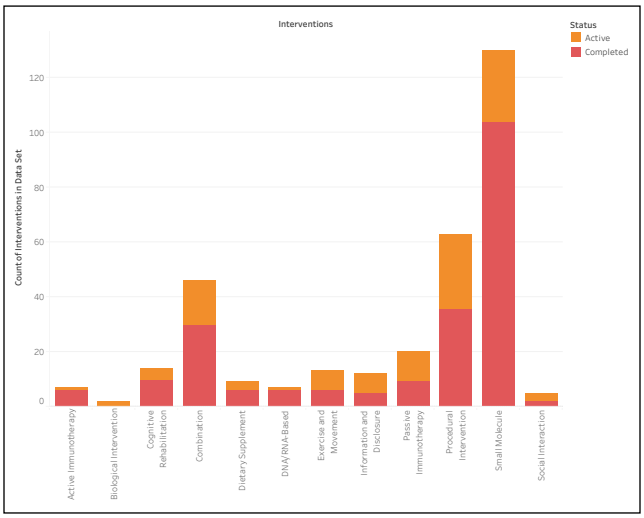

Figure 2. Intervention comparisons between past and current clinical trials and therapeutic interventions in Alzheimer's disease

1, the "evidence map", identifies gaps and developments within the interventions and their relationships to common outcome measures, such as cognitive assessments or pharmacokinetics. Intervention categories were also compared, based solely on the Categorical definitions subsection (Figure 2). Due to the quantitative difference between pending and completed denominators, percentages were contrasted throughout the study for the specific intervention types. Each of these percentages were documented in individual sections of intervention comparisons. Figure 2 was created through the Tableau Public, a desktop software for data visualization.

Categorical Definitions

Intervention categorizations were conducted through definitions from ClinicalTrials.Gov, The Agency of Healthcare Research and Quality (AHRQ), and the AlzForum Therapeutics Database.[24,25] AlzForum's updated therapeutics database provided most information for pharmaceutical and procedural intervention types in dementia, cognitive impairment, and AD. Specific drugs and molecules were classified under the pharmaceutical interventions listed below. Three overarching sections for interventions were chosen, based on the guidelines presented by the references listed above: pharmaceutical and biological, procedural, and behavioural.

The various behavioural interventions included "Exercise and movement", "Information and disclosure", "Cognitive rehabilitation", and "Social interaction" (Table 2).

The categories of pharmaceutical and procedural interventions followed the therapeutics database of AlzForum, an information-based website to support researchers, in terms of drug discovery and treatment. These categories were "Combination", "DNA/RNA-based", "Active immunotherapy", "Passive immunotherapy", "Small molecule", "Biological intervention", "Dietary supplement", and "Procedural intervention" (Table 3).

Table 2. Categorical definitions for behavioural interventions

Exercise and movement	Activity-based interventions that support stabilization of neuropsychiatric symptoms, such as anxiety, aggression, or depression. Examples include dancing or cardio-based exercises every morning over a sample time period.
Information and disclosure	Disclosure of Alzheimer's disease (AD)-related symptoms or risk factors and education platforms for patients and families. This category usually directs the information and disclosure towards patients rather than caregivers, who are already informed regarding the function of the individual with cognitive impairment.
Cognitive rehabilitation	Cognitive rehabilitation therapy (CRT) is a psychological therapy for thought patterns, memory, and relaxation. CRT has been demonstrated to combat cognitive deterioration through non-invasive methods in individuals with neuropsychiatric disorders and/or criminal behaviours, pregnant mothers, and elderly adults.[26]
Social interaction	Communication through clinical trials with caregivers, other patients (with or without dementia), and professional support to improve social skills, quality of life, and neuropsychiatry for patients with AD.

Intervention comparisons

Active and Passive Immunotherapy

The diminished size of active trials describes the failures of active immunotherapy (Figure 2). The last active immunotherapeutic intervention, AN-1792, consisted of a synthetic Aβ peptide and showed varied promise through the trial's initial phases. However, it was terminated in Phase 3 due to treatment-emergent cerebral inflammation in 6% of patients.[37,38] Three active immunotherapies (AD02, ACC-001, and CAD106) were shut down by pharmaceutical corporations due to treatment-emergent symptoms, tolerability and safety, or minimal cognitive success.[39]

Table 3. Categorical definitions for pharmaceutical and procedural interventions

Combination	Two or more interventions tested in one clinical trial. Examples include pairings of behavioural and pharmaceutical interventions to combine invasive and non-invasive approaches or cross-over and factorial study designs to interchange intervention assignment. This category was not analyzed due to minimal developments and relevance of combinatorial therapy.
DNA/RNA-based	Personalized medicine is the synthesis of precise molecules based on specific genomic sequences. Examples include antisense oligonucleotides (ASOs) and RNA interference (RNAi), which target specific mRNA strands and control protein production.27 This has shown extensive potential for tau protein and even other neurodegenerative diseases, such as Huntington's.[28]
Active immunotherapy	Methods engaging the host's immune system (in this case, the patient's) through molecular stimulation that amounts to an eventual response.[29]
Passive immunotherapy	Immune system-related molecules without activation or engagement of the immune system. Passive and active immunotherapy differ based on immune system involvement.[29]
Small molecule	Targeted small molecule therapies, organic molecules with low molecular weights actively targeting specific biomarkers.[30] In Alzheimer's disease trials, small molecules are synthesized to degrade amyloid-beta plaques, tau-based neurofibrillary tangles, or other biomarkers. Examples include secretase inhibitors to prevent the improper cleavage of the amyloid precursor protein.[31]
Biological intervention	Substances created from living organisms to treat neurodegenerative diseases. The only examples in the data set were mesenchymal stem cells (MSCs) derived from mesodermal embryonic regions to promote regenerative measures. MSCs are the primary focus of neurodegenerative stem cell therapy due to their multipotency rather than the regional limitations of other stem cells.[32-34]
Dietary supplement	Additions to daily routines for patients during a trial, usually in the form of pills or capsules. Examples include turmeric derivatives that contain phenolic compounds supporting disaggregation of amyloidogenic plaques.[35]
Procedural intervention	Imaging studies and device-based interventions that use energy sources to stimulate brain activity. Examples include transcranial magnetic stimulation, which conducts electromagnetic currents in patients exhibiting neuropsychiatric symptoms, or positron emission tomography tracers for plaque imaging.[36]

Passive immunotherapy demonstrates high tolerability and safety, even though only a few clinical trials have shown evidence demonstrating substantially slower cognitive decline rates.[40,41] Additional research regarding the introduction of antibodies has shown promise in Phase 1 and Phase 2 trials. Through proposed hypotheses, such as phagocytosis and toxic neutralization, synthetic antibodies are expanding current trials (Figure 2).[39]

Monoclonal antibodies (mABs) have become the focal point of passive immunotherapy in pending trials. These agents, mABs, are cloned antibodies from one unique parent immune cell, which can either be completely human or humanized. Humanized antibodies are taken from organisms and synthesized through human-adjusted variants, while complete human mABs are taken from humans or similar organisms with minimal modifications.[42] Multiple researchers hypothesize mABs could counteract Aβ oligomers through microglial activation, preventing neuronal degeneration.[43]

Eleven different passive immunotherapies are being tested for brain amyloid clearance, safety, and tolerability in pending trials. BAN2401, a humanized mAB-based drug currently in Phase 2 trials, resulted in 93% brain amyloid removal in the highest-dose group, along with 30-50% decreased cognitive decline.[44] Gosuranemab is an anti-tau mAB that decreased tau NFT formation by 67 to 97%; further drug analysis is required for tolerability, safety, and pharmacokinetics.[45] Current trials on semorinemab, another humanized tau mAB, are being conducted in Phase 2 after successful safety and hazard testing.[46] Additional passive immunotherapeutics in active trials are heavily supported by mAB precedent, including Donanemab, Gantenerumab, and Crenezumab.[40]

DNA/RNA-based therapies (precision/personalized medicine)

Precision medicine develops tailored drugs and interventions for individual patients. Past therapies included the use of albumin, immunoglobulin, and insulin in multiple trials as potential methods for slowing cognitive impairment; however, molecular cross-applicability failed to slow cognitive decline after strong safety and patient tolerability protocols.[47-50] Current research for individualized therapies revolves around gene therapy and antisense oligonucleotides. Vector-driven expression of the nerve growth factor (NGF) in the CERE-110 gene therapy trial was discontinued due to results with minimal effect on cognitive impairment.[51] Antisense oligonucleotides (ASOs) are synthesized based on nucleotide sequences; through complementary replication, ASOs can prevent gene expression and protein production. ASOs have had success with genetic neurological disorders such as Duchenne muscular dystrophy, which refers to a single DMD gene.[52] Figure 2 identifies only one ASO-based clinical trial of IONIS-MAPTRx, an anti-tau therapy in Phase 1 trials targeting specific mRNA strands involved in tau protein production causing neuropathic disorders.[53]

Personalized therapies have likely decreased due to the challenges of individualized medicine. The examination of genetic variation is critical to understand and innovate personalized medicine.[54] Currently, the clinical knowledge of genetic causes of AD are unknown, making DNA/RNA-based therapies difficult. While the one-size-fits-all models hold disadvantages, they have the potential to slow cognitive decline in multiple patients compared to in a single individual. Additionally, the costs associated with DNA sequencing, hyper-specific molecular development, third-party medical premiums, and medical regulatory guidelines discourage pharmaceutical interest in precision medicine.[55]

Specific mutated genotypes associated with AD and cognitive impairment continue to offer promise for individualized medicine. As genetic analysis grows, the expansion of causal relationships between genotypes and AD is imminent, offering affordable methods for pharmaceutical companies.[56]

Biological Intervention

As described in the Categorical definitions subsection, mesenchymal stem cell(MSC) therapy is the primary focus of the biological interventions developed in only pending trials (Figure 2). MSC therapies focus specifically on neurodegenerative diseases through production of growth factors for neural regeneration in the host patient.[57] Both Phase 1 clinical trials are currently investigating safety and tolerability protocols.[32,33] Neurodegenerative stem cell

therapy remains to be heavily researched due to the complexities of neurologic pathways. Preclinical studies have found that the translation from animal to human models in stem cell therapy, especially considering neurological conditions, has been inaccurate. Transgenic models present different genetics with homogeneous populations based on hypotheses, whereas humans affected by AD span a spectrum of heterogeneity in terms of race, gender, ethnicity, and other genetics-related factors.[34] Exogenous and endogenous methods of stem cell therapy present simultaneous limitations. Endogenous reparation in AD fails due to minimal neural regeneration.[59] AD is associated with major neural degeneration of the CA1 subregion in the hippocampus, and stem-cell-induced hippocampal regeneration fails to restore neural connections in CA1. Exogenous introductions of stem cells risk tumour formation because of nonnatural stem cells.[58] Specific cell therapies, such as embryonic stem cell therapies (ESCs), present ethical challenges due to different donor cells; however MSCs and induced pluripotent stem cells (iPSCs) have potential to circumvent concerns due to regenerative multipotency, including neurotransmission and neuroprotection.[59,60]

The multipotency of MSCs remains the most enticing development in AD clinical trials, but also encourages research into specific stem cell therapies targeting specific brain structures, such as the dentate gyrus in the case of brain-derived neural stem cell therapies (NSCs).[34]

Procedural Intervention

Procedural interventions slightly increased in trial popularity, likely due to safe, inexpensive, and non-invasive methods regarding stimulation, brief energetic repetitions controlling action potentials in neurons, and manipulating brain activity in tested patients (Figure 2).[61] The focal points of device-based and procedural interventions are neural and brain region-based stimulation. Neural stimulation includes energy sources, such as airway pressure, light waves, radiation, and magnetic fields.

Continuous positive airway pressure (CPAP) is used for sleep-related and neuropsychiatric conditions, which are extensively linked to AD pathogenesis.[62] Mixed results regarding CPAP and cognitive impairment have been reported; however the quality of life, mood, and sleep assessments associated with CPAP interventions are positive, with decline in obstructive sleep apnea.[62] Ongoing investigations are likely to develop studies and technologies temporarily managing symptoms to improve living standards for patients with AD.

Transcranial stimulation is another research focus for device-based interventions and has shown potential modulation and regulation for neuropsychiatric diseases.[63] AD research presented in this interventional review regarding transcranial stimulation has focused on the non-invasive brain stimulation techniques. Of the seven trials pertaining to transcranial stimulation in this review, the categories of non-invasive transcranial stimulation are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS). Other methods such as transcranial alternating current stimulation (TACS) have also been conducted in vitro, reporting lower connectivity in neuronal function and decreased modulation; the failures during in vitro testing are presumably the reason why TACS is not represented in this interventional review's clinical trial data.[77] TMS utilizes electromagnetic stimulation in energetic bursts directed to motor and cognitive regions to reduce depression, psychosis, and neuropsychiatric symptoms associated with AD.[63] Systematic reviews identify TMS with positive results on cognitive assessments, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale.[64] Further TMS development could provide cost-effective, non-invasive approaches, maximizing accessibility. TDCS serves as a different modulatory technique that delivers constant, low-powered currents; this is almost the opposite of the energetic bursts of TMS. TDCS has improved symptoms of patients with AD, especially in task-based assessments such as word recognition and face-name association.[78]

Other forms of neural stimulation are categorized based on energy source. New energy-based methods, including infrared, gamma ray, and other energetic stimulations, can manipulate plaque deposition in non-invasive approaches, having success in preliminary in vivo trials.65 Gamma ray stimulation reduced tau and amyloid biomarkers in a small-scale human study.[66] Stimulatory methods could expand device-based interventions with minimal risk, resolving a plethora of neuropsychiatric concerns.

Behavioural Intervention

Current behavioural interventions have nearly doubled in comparison to completed trials (Figure 2). Behavioural interventions present minimal requirements for in vivo and in vitro models, which are likely associated with the expansion of the field. 80-90% of patients with cognitive impairment or AD pathogenesis present neuropsychiatric symptoms, establishing the need for behavioural methods to improve and sustain quality of life.[67] Studies continue to conclude that symptom management is best through social interaction and caregiver training compared to antidepressants and antipsychotic medications.[68] As pharmaceutical approaches are deemed ineffective and unsafe, behavioural intervention remains the safest and most tolerable method for symptom management, especially when measuring long-term outcomes post-trial (Table 1).[69] Each of the subcategories listed under the Categorical definitions subsection had percentage increases in clinical interventions. Disclosure and educational services given to families and patients, when supported with accurate assessments, have improved neuropsychiatry; resulting neuropsychiatry can vary when assessment evaluations are ambiguous and lack sufficient information for direct diagnosis.[70] With additional neuroimaging studies to identify cause-effect relationships between biomarkers, information, and AD, information and disclosure will expand as assessments are able to make accurate diagnoses. Exercise and movement are common interventions in many disorders, ranging from obesity to cognition-related disorders. Exercise is directly related to tissue oxygenation within the brain, which has been shown to improve AD symptom management in similar methods as CPAP, due to the similarities in oxygen delivery mechanisms.[71] Social interaction and cognitive rehabilitation follow similar patterns in neuropsychiatric symptom management.[72,73]

Small Molecule

Quite possibly the most important pharmaceutical therapeutic of all remains the small molecule method. Small molecule treatments have decreased significantly, possibly due to the plethora of Phase 3 trial failures (Figure 2). Much of this can be attributed to differences in transgenic models, as mentioned in Biological

interventions, causing multiple treatment-emergent symptoms. Avagacestat, a gamma-secretase inhibitor focused on the proper cleavage of APP, failed to pass safety and tolerability tests in Phase 2 due to higher doses causing progression of skin cancer along with nausea.[39] Clioquinol, a cross-applied molecule designed for the disruption between toxic metals and amyloidogenic peptides in the brain, was reported to have no evidence of safety or efficacy.[74] The AlzForum Therapeutics Database details tens of treatments that are inactive, shelved, or discontinued.[25] While the small molecule intervention section is the most populous amongst completed clinical trials, the decreased research concentration on small molecules is associated with lack of outcome standardization (Table 1), decreased focus on drug kinetics and uptake (better known as pharmacokinetics), inability to establish causal relationships between drugs, biomarkers, and AD, and transgenic inaccuracies.[75]

All in all, the trends described by the data evidently recognize the advancements and the shortcomings of certain therapies in the AD pipeline. The findings of the interventional review examined the past changes in research directions in order to establish potential research directions in the future. Moreover, the various categories each provide a snapshot of the trial analyses since 2005. The vast field of therapeutics provides opportunities for researchers to explore different aspects of AD, especially in regard to the NIA-AA framework's conclusions of biomarkers. The categorical therapies discussed all contribute to the considerable effect of AD biomarkers and the progression in plaque deposition, whether through pharmaceutical, behavioural, or procedural methods.

Discussion

Through the entire systematic review process, the study report focused on comparisons between past and current trials, analyzing differences in therapeutic categories. The development of relatively new therapeutic methods, such as behavioural interventions, passive immunotherapy, and various potent stem cell therapies, have shown promise to slow cognitive decline, and potentially manage symptoms and reverse the pathogenesis of AD. MSC therapies and mABs are currently in early trial phases for safety and tolerability, with potential to degrade commonly associated biomarkers, such as hyperphosphorylated tau and amyloidogenic peptides. The consistency of behavioural interventions is additionally noted amongst researchers, representing a non-invasive, neuropsychiatric approach to symptom management, as clinicians research potential pharmaceutical and biological methods. Precision and individualized medicine remains to be heavily researched as pharmaceutical companies look for methods to reduce biomarkers for entire experimental groups rather than individuals. As traditional treatments, such as small molecules and active immunotherapy, fail to produce substantial differences in cognitive decline and AD-related symptoms and slowly phase out, novel methods including device-based interventions could provide valuable insight into brain structures, symptom-biomarker-pathogenesis relationships, and effective therapies to improve neuropsychiatric symptoms and reverse cognitive dysfunction.

Limitations

As mentioned beforehand, the limitations regarding clinical trial registries could represent a possible impediment due to the significant issues concerning data reporting. While the ClinicalTrials.Gov registry has diverse trials from across the globe, 6% of a sample set of 347 trials were reported in ClinicalTrials.Gov; a significant example of potential discrepancies for clinical trials in AD.[76] With 24 different clinical trial registries, the lack of standardized reporting methods was a major cause of the disparities presented in the interventional review. Differences in symptoms related to ethnicity, race, and other biogeography-related factors could change the landscape of therapeutic evaluation and assessment, as the success of interventions may be affected by the presentation of genetic factors that are relevant in specific ethnicities, for example. Moreover, the exclusion of other international trials and the unavailability of the ICTRP could change the comparisons of each intervention category.

Future directions

Future directions of research could involve the investigations of clinical trials in AD in multiple international registries, such as the ICTRP and European Union Clinical Trials Register, to encompass more details, interventions, and additional categories that ClinicalTrials.Gov may have not been exposed to beforehand. Moreover, researchers could utilize this analysis to determine future projects in the therapy development pipeline for investigating biomarkers and causes of AD. Analyzing outcome measurements in AD clinical trials, the popularity of specific assessments, and the lack of standardization available could also be a future direction of research that could prove as valuable as the intervention analysis conducted within this report.

Acknowledgements

Thank-you to Dr. Spencer Hey, Faculty Member at Harvard University Medical School Center of Bioethics, for the contributions during the review and editing process. Thank you to UTMJ for reviewing the submission.

Views and hypotheses supported are not representative of affiliated organizations; all views are based on the opinions and perspectives of cited papers and respective authors. The author conducted all research and manuscript preparation for submission to UTMJ; no funding sources were utilized to support this report's production or influence any perspectives. The author additionally declares no conflicting interests with the information presented.

References

1. Patterson C. World Alzheimer's Report 2018 [Internet]. London; 2018 [cited 2020 Nov 15]. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf.
2. Meek PD, McKeithan EK, Schumock GT. Economic considerations in Alzheimer's disease. Pharmacotherapy. 1998 Mar-Apr;18(2 Pt 2):68-73; discussion 79-82. PMID: 9543467.
3. Deb A, Thornton JD, Sambamoorthi U, et al. Direct and indirect cost of managing Alzheimer's disease and related dementia in the United States. Expert Rev Pharmacoecon Outcomes Res. 2017 Apr;17(2):189-202. doi: 10.1080/14737167.2017.1313118.
4. Watson JL, Ryan L, Silverberg N, et al. Obstacles and opportunities in Alzheimer's clinical trial recruitment. Health Aff (Millwood). 2014 Apr;33(4):574-9. doi:10.1377/hlthaff.2013.1314.
5. FDA-Approved Treatments for Alzheimer's [Internet]. Alzheimer's Association; 2019 [cited 2020 Nov 15]. Available from: https://www.alz.org/media/documents/fda-approved-treatments-alzheimers-ts.pdf.
6. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 2014 Apr;71(4):505-8. doi: 10.1001/jamaneurol.2013.5847. PMID: 24493463.
7. den Haan J, Morrema TH, Verbraak FD, et al. Amyloid-beta and phosphorylated tau in post-mortem Alzheimer's disease retinas. Acta Neuropathol Commun. 2018 Dec 28;6(1):147. doi: 10.1186/s40478-018-0650-x.

8. Kametani F, Hasegawa M. Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. Front Neurosci. 2018 Jan 30;12:25. doi:10.3389/fnins.2018.00025.
9. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer's disease. Indian J Psychiatry. 2009 Jan;51(1):55-61. doi: 10.4103/0019-5545.44908.
10. Makin S. The amyloid hypothesis on trial. Nature. 2018 Jul;559(7715):S4-S7. doi: 10.1038/d41586-018-05719-4.
11. McGeer EG, McGeer PL. Neuroinflammation in Alzheimer's disease and mild cognitive impairment: a field in its infancy. J Alzheimers Dis. 2010;19(1):355-61. doi: 10.3233/JAD-2010-1219.
12. Clements A, Allsop D, Walsh DM, et al. Aggregation and metal-binding properties of mutant forms of the amyloid A beta peptide of Alzheimer's disease. J Neurochem. 1996 Feb;66(2):740-7. doi: 10.1046/j.1471-4159.1996.66020740.x.
13. Norris CM, Kadish I, Blalock EM, et al. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. J Neurosci. 2005 May 4;25(18):4649-58. doi: 10.1523/JNEUROSCI.0365-05.2005.
14. FDA approves memantine drug for treating AD. Am J Alzheimers Dis Other Demen. 2003 Nov-Dec;18(6):329-30. PMID: 14682078.
15. Life Molecular Imaging SA. Florbetaben (BAY94-9172) PET (positron emission tomography) imaging in MCI (mild cognitive impairment) patients [Internet]. ClinicalTrials.gov; 2010 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01138111.
16. Avid Radiopharmaceuticals. Evaluation of PET scan timing relative to AV-45 injection time [Internet]. ClinicalTrials.gov; 2012 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01565356.
17. Life Molecular Imaging SA. An open-label, non-randomized, multi-center study to optimize image assessment and evaluate the efficacy and safety of BAY-949172 (ZK 6013443) positron emission tomography (PET) for detection/exclusion of cerebral amyloid beta in patients with probable Alzheimer's disease compared to healthy volunteers [Internet]. ClinicalTrials.gov; 2008 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00750282.
18. Vaquero JJ, Kinahan P. Positron emission tomography: Current challenges and opportunities for technological advances in clinical and preclinical imaging systems. Annu Rev Biomed Eng. 2015;17:385-414. doi: 10.1146/annurev-bioeng-071114-040723.
19. James OG, Doraiswamy PM, Borges-Neto S. PET imaging of tau pathology in Alzheimer's disease and tauopathies. Front Neurol. 2015 Mar 9;6:38. doi: 10.3389/fneur.2015.00038.
20. Higgins JP, Lasserson T, Chandler J, et al. Standards for the conduct of new Cochrane Intervention Reviews [Internet]. Cochrane Library; 2020 [cited 2020 Nov 15]. Available from: https://community.cochrane.org/mecir-manual.
21. Glanville JM, Duffy S, McCool R, et al. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: What are the optimal search approaches? J Med Libr Assoc. 2014 Jul;102(3):177-83. doi: 10.3163/1536-5050.102.3.007.
22. Critical appraisal skills programme randomised controlled trial checklist [Internet]. CASP; 2018 [cited 2020 Nov 15]. Available from: https://casp-uk.net/casp-tools-checklists/.
23. Preferred reporting items for systematic reviews and meta-analyses flow diagram [Internet]. PRISMA; 2015 [cited 2020 Nov 15]. Available from: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx.
24. Non-Pharmacologic Interventions for Agitation and Aggression in Dementia [Internet]. Effective Health Care Program of the Agency for Healthcare Research and Quality; 2014 Nov 13 [cited 2020 Nov 15]. Available from: https://effectivehealthcare.ahrq.gov/products/dementia-agitation-aggression/research-protocol.
25. Therapeutics [Internet]. AlzForum; 2020 June [cited 2020 Nov 15]. Available from: https://www.alzforum.org/therapeutics.
26. Hofmann SG, Asnaani A, Vonk IJ, et al. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cognit Ther Res. 2012 Oct 1;36(5):427-440. doi: 10.1007/s10608-012-9476-1.
27. Verma A. Recent advances in antisense oligonucleotide therapy in genetic neuromuscular diseases. Ann Indian Acad Neurol. 2018 Jan-Mar;21(1):3-8. doi: 10.4103/aian.AIAN_298_17.
28. Carroll JB, Warby SC, Southwell AL, et al. Potent and selective antisense oligonucleotides targeting single-nucleotide polymorphisms in the Huntington disease gene/allele-specific silencing of mutant huntingtin. Mol Ther. 2011 Dec;19(12):2178-85. doi: 10.1038/mt.2011.201.
29. Brody DL, Holtzman DM. Active and passive immunotherapy for neurodegenerative disorders. Annu Rev Neurosci. 2008;31:175-93. doi: 10.1146/annurev.neuro.31.060407.125529.
30. Ngo HX, Garneau-Tsodikova S. What are the drugs of the future? Medchemcomm. 2018 Apr 23;9(5):757-758. doi: 10.1039/c8md90019a.
31. Cusulin C, Wells I, Badillo S, et al. Gamma secretase modulators and BACE inhibitors reduce Aβ production without altering gene expression in Alzheimer's disease iPSC-derived neurons and mice. Mol Cell Neurosci. 2019 Oct;100:103392. doi: 10.1016/j.mcn.2019.103392.
32. Longeveron LLC. A phase I prospective, randomized, double-blinded, placebo-controlled, trial to evaluate the safety and potential efficacy of Longoveron allogeneic human mesenchymal stem cell (LMSCs) infusion versus placebo in patients with Alzheimer's disease [Internet]. ClinicalTrials.gov; 2015 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02600130.
33. Hope Biosciences. A clinical trial to determine the safety and efficacy of Hope Biosciences autologous mesenchymal stem cell therapy (HB-AdMSCs) for the treatment of Alzheimer's disease [Internet]. ClinicalTrials.gov; 2020 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04228666.
34. Duncan T, Valenzuela M. Alzheimer's disease, dementia, and stem cell therapy. Stem Cell Res Ther. 2017 May 12;8(1):111. doi: 10.1186/s13287-017-0567-5.
35. den Haan J, Morrema TH, Rozemuller AJ, et al. Different curcumin forms selectively bind fibrillar amyloid beta in post mortem Alzheimer's disease brains: Implications for in-vivo diagnostics. Acta Neuropathol Commun. 2018 Aug 9;6(1):75. doi: 10.1186/s40478-018-0577-2.
36. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002 Mar;5(1):73-103. doi: 10.1017/S1461145702002791.
37. Huang LK, Chao SP, Hu CJ, et al. Clinical Trials of New Drugs for Alzheimer Disease. J Biomed Sci. 2020 Jan 6;27(1):18. doi:10.1186/s12929-019-0609-7.
38. Gilman S, Koller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology. 2005 May 10;64(9):1553-62. doi: 10.1212/01.WNL.0000159740.16984.3C.
39. Moreth J, Mavoungou C, Schindowski K. Passive anti-amyloid immunotherapy in Alzheimer's disease: What are the most promising targets? Immun Ageing. 2013 May 11;10(1):18. doi: 10.1186/1742-4933-10-18.
40. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: an update. J Cent Nerv Syst Dis. 2020 Feb 29;12:1179573520907397. doi: 10.1177/1179573520907397.
41. Doggrell SA. Grasping at straws: the failure of solanezumab to modify mild Alzheimer's disease. Export Opin Biol Ther. 2018 Dec;18(12):1189-1192. doi: 10.1080/14712598.2018.1543397.
42. Prins ND, Scheltens P. Treating Alzheimer's disease with monoclonal antibodies: current status and outlook for the future. Alzheimers Res Ther. 2013 Nov 11;5(6):56. doi: 10.1186/alzrt220.
43. Zahner SP, Wilkinson N, Nguyen C, et al. Development of two novel microglia-specific monoclonal antibodies to discriminate microglia from other CNS-resident macrophages by flow cytometry. J Immunol. 2020 May 1;204:86.53.
44. BAN2401 [Internet]. AlzForum; 202015 [cited 2020 Nov 15]. Available from: https://www.alzforum.org/therapeutics/ban2401.
45. Qureshi IA, Tirucherai G, Ahlijanian MK, et al. A randomized, single ascending dose study of intravenous BIIB092 in healthy participants. Alzheimers Dement (N Y). 2018 Dec 17;4:746-755. doi: 10.1016/j.trci.2018.10.007.
46. Genentech Incorporated. A phase 1, randomized, placebo-controlled, double-blind, single and multiple ascending dose study to assess the safety, tolerability, and pharmacokinetics of intravenous and subcutaneous RO7105705 administered in healthy volunteers and patients with mild-to-moderate Alzheimer's disease [Internet]. ClinicalTrials.gov; 2016 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02820896.
47. Sutter Health. A randomized double-blinded placebo-controlled exploratory study of intravenous immunoglobulin (NewGam 10%) in amnestic mild cognitive impairment [Internet]. ClinicalTrials.gov; 2011 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01300728.
48. Octapharma. Prospective 24-week, double-blind, randomised, placebo-controlled, multicenter study evaluating safety and change in efficacy-related surrogate parameters in patients with dementia of the Alzheimer's type under treatment with increasing dosages of intravenous immunoglobulin (Octagam 10%) [Internet]. ClinicalTrials.gov; 2008 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00812565.
49. Instituto Grifols. A study to evaluate albumin and immunoglobulin in Alzheimer's disease [Internet]. ClinicalTrials.gov; 2019 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01561053.
50. Bosco D, Fava A, Plastino M, et al. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med. 2011 Sep;15(9):1807-21. doi: 10.1111/j.1582-4934.2011.01318.x.
51. CERE-110 [Internet]. AlzForum; 2015 [cited 2020 Nov 15]. Available from: https://www.alzforum.org/therapeutics/cere-110.
52. Rinaldi C, Wood MJ. Antisense oligonucleotides: the next frontier for treatment of neurological disorders. Nat Rev Neurol. 2018 Jan;14(1):9-21. doi: 10.1038/nrneurol.2017.148.
53. Ionis Pharmaceuticals. A randomized, double-blind, placebo-controlled study, followed by an open-label extension, to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of intrathecally administered ISIS 814907 in patients with mild Alzheimer's disease [Internet]. ClinicalTrials.gov; 2017 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03186989.
54. Ramos E, Callier SL, Rotimi CN. Why personalized medicine will fail if we stay the course. Per Med. 2012 Nov;9(8):839-47. doi: 10.2217/pme.12.100.

55. What are some of the challenges facing precision medicine and the Precision Medicine Initiative? [Internet]. Genetics Home Reference; 2015 [cited 2020 Nov 15]. Available from: https://ghr.nlm.nih.gov/primer/precisionmedicine/challenges.
56. Ryan L, Hay M, Huentelman MJ, et al. Precision aging: Applying precision medicine to the field of cognitive aging. Front Aging Neurosci. 2019 Jun 7;11:128. doi: 10.3389/fnagi.2019.00128.
57. Chen L, Qiu R, Xu Q. Mesenchymal stem cell therapy for neurodegenerative diseases. J Nanosci Nanotechnol. 2014 Jan;14(1):969-75. doi: 10.1166/jnn.2014.9126.
58. Fong CY, Gauthaman K, Bongso A. Teratomas from pluripotent stem cells: A clinical hurdle. J Cell Biochem. 2010 Nov 1;111(4):769-81. doi: 10.1002/jcb.22775.
59. Munoz JR, Stoutenger BR, Robinson AP, et al. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. Proc Natl Acad Sci U S A. 2005 Dec 13;102(50):18171-6. doi: 10.1073/pnas.0508945102.
60. Pang ZP, Yang N, Vierbuchen T, et al. Induction of human neuronal cells by defined transcription factors. Nature. 2011 May 26;476(7359):220-3. doi: 10.1038/nature10202.
61. Vosskuhl J, Strüber D, Hermann CS. Non-invasive brain stimulation: A paradigm shift in understanding brain oscillations. Front Hum Neurosci. 2018 May 25;12:211. doi: 10.3389/fnhum.2018.00211.
62. Richards, KC. Mild cognitive impairment and obstructive sleep apnea [Internet]. ClinicalTrials.gov; 2011 [cited 2020 Nov 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01482351.
63. Ahmed MA, Darwish ES, Khedr EM, et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol. 2012 Jan;259(1):83-92. doi: 10.1007/s00415-011-6128-4.
64. Dong X, Yan L, Huang L, et al. Repetitive transcranial magnetic stimulation for the treatment of Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2018 Oct 12;13(10):e0205704. doi: 10.1371/journal.pone.0205704.
65. Zhang Y, Wang F, Luo X, et al. Cognitive improvement by photic stimulation in a mouse model of Alzheimer's disease. Curr Alzheimer Res. 2015;12(9):860-9. doi: 10.2174/1567205012666150710115755.
66. Jones M, McDermott B, Oliveira BL, et al. Gamma band light stimulation in human case studies: Groundwork for potential Alzheimer's disease treatment. J Alzheimers Dis. 2019;70(1):171-185. doi: 10.3233/JAD-190299.
67. Nowrangi MA, Lyketsos CG, Rosenberg PB. Principles and management of neuropsychiatric symptoms in Alzheimer's dementia. Alzheimers Res Ther. 2015 Jan 29;7(1):12. doi: 10.1186/s13195-015-0096-3.
68. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015 Mar 2;350:h369. doi: 10.1136/bmj.h369.
69. Liebowitz MR, Heimberg RG, Schneier FR, et al. Cognitive-behavioral group therapy versus phenelzine in social phobia: long-term outcome. Depress Anxiety. 1999;10(3):89-98. PMID: 10604081.
70. Smith AP, Beattie BL. Disclosing a diagnosis of Alzheimer's disease: patient and family experiences. Can J Neurol Sci. 2001 Feb;28 Suppl 1:S67-71. doi: 10.1017/s0317167100001220.
71. Lu X, Moeini M, Li B, et al. Voluntary exercise increases brain tissue oxygenation and spatially homogenizes oxygen delivery in a mouse model of Alzheimer's disease. Neurobiol Aging. 2020 Apr;88:11-23. doi: 10.1016/j.neurobiolaging.2019.11.015.
72. Hsiao YH, Chang CH, Gean PW. Impact of social relationships on Alzheimer's memory impairment: mechanistic studies. J Biomed Sci. 2018 Jan 11;25(1):3. doi: 10.1186/s12929-018-0404-x.
73. Germain S, Wojtasik V, Lekeu F, et al. Efficacy of cognitive rehabilitation in Alzheimer disease: A 1-year follow-up study. J Geriatr Psychiatry Neurol. 2019 Jan;32(1):16-23. doi: 10.1177/0891988718813724.
74. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's dementia. Cochrane Database Syst Rev. 2014 Feb 21;(2):CD005380. doi: 10.1002/14651858.CD005380.pub5.
75. Becker RE, Greig NH, Giacobini E. Why do so many drugs for Alzheimer's disease fail in development? Time for new methods and new practices? J Alzheimers Dis. 2008 Oct;15(2):303-25. doi: 10.3233/jad-2008-15213.
76. Glanville JM, Duffy S, McCool R, et al. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? J Med Libr Assoc. 2014 Jul;102(3):177-183. doi: 10.3163/1536-5050.102.3.007.
77. Abellaneda-Perez K, Vaque-Alcazar L, Perellon-Alfonoso R, et al. Differential tDCS and tACS Effects on Working Memory-Related Neural Activity and Resting-State Connectivity. Front Neurosci. 2020 Jan 17;13:1440. doi: 10.3389/fnins.2019.01440.
78. Chang CH, Lane HY, Lin CH. Brain Stimulation in Alzheimer's Disease. Front Psychiatry. 2018 May 22;9:201. doi: 10.3389/fpsyt.2018.00201.
79. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018 Apr;14(4):535-562. doi: 10.1016/j.jalz.2018.02.018.