Examining The Current State of Alzheimer's Disease Research and Exploring the Potential Benefit of Expanding the Use of Telemedicine in Diagnosis, Monitoring and Treatment

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Received October 13, 2024
Accepted December 29, 2024
Electronic access January 15, 2024

Alzheimer's Disease (AD) is the most prominent form of dementia worldwide, with its prevalence rising as the global population ages. Its irreversibility and incurability make it the seventh leading cause of death in the US in 2023. Previous research has proposed several mainstream theories on AD's pathogenic mechanisms and designed medications to some efficacy. Despite AD's debilitating nature, early prevention, detection, and treatment are positively associated with later onset, prolonged progression, and better cognitive abilities; therefore, early diagnosis is at the crux of improving AD patients' average survival rate and life quality. This article reviews contemporary literature on recent advancements in AD research, specifically addressing the clinical manifestation and diagnosis of AD, as well as the mainstream hypotheses regarding its pathophysiology. Additionally, the article will explore cutting-edge research areas, such as the roles of microglia and Notch receptors, and discuss future treatment directions, including stem cell therapy, music therapy, and the use of telemedicine for AD diagnosis, monitoring, and treatment. The initial review includes more than 200 relevant articles using but not limited to keywords listed below, and excludes articles that contain out-dated conclusions, flawed methodological designs, or small sample size. Each article reviewed is categorized into themes (i.e. clinical manifestation, pathophysiology, treatment approach, etc.), and only relevant data and conclusions are extracted. This review's finding suggests the immense potential of telemedicine in AD diagnosis and treatment, delaying disease progression and increasing life quality.

Keywords: Alzheimer's Disease (AD), Amyloid beta, APOE4, Neuroinflammation, Early Diagnosis, Clinical Manifestation, Music therapy, Telemedicine

Introduction

Dementia, characterized by memory loss, impaired cognitive ability, and limited social skills, is an umbrella term for a wide array of neurodegenerative diseases, including vascular dementia, Huntington's disease, and Lewy Body dementia[1]. Among all, AD is the leading cause of dementia, accounting for 60 to 80 percent of all dementia cases[2]. AD is a progressive, neurodegenerative disease that, in addition to dementia, causes memory loss, and changes in personality, along with a host of other biological and psychological changes[3]. The World Health Organization reported that in 2020, over 50 million of the population aged above 60 lived with dementia, in which AD is the most common cause. Doubling every 20 years, AD incidence is estimated to triple to 14 million in 2060[4]. The regional prevalence of AD is quite significant, with the lowest incidence rate of 1.6% in Africa and the highest of 6.4% in North America[5]. This significant decrease in incidences most likely stems from the shorter average lifespan in Africa (64.11) given that AD typically develops in one's 70's and 80's. In contrast, within the U.S., over half of the population lives to 75, which opens the door for the disease to show physical symptoms. Thus, it is worth considering the effect of lifespan differences on AD diagnosis and prevelance. Due to the existence of factors like limited populations of minority groups in AD research and biases in testing language or content, these results require further confirmation[6].

AD progression and severity can be described using a variety of classification systems including the Braak's criterion and the Consortium to Establish a Registry for Alzheimer's disease (CERAD) criterion, which examines neurofibrillary tangles density in the whole brain and the density of neocortical plaques, respectively[7]. Interestingly, despite scientists' thorough research and constant effort in Aβ and tau, there are limited treatments for AD. This suggests that researchers still have not yet comprehended the whole picture of AD pathogenesis, and thus, investigating alternative cellular pathways that may be involved in the symptoms associated with AD remains important.

The early diagnosis of AD is difficult not only because it can be only confirmed by autopsy but also because of the stigma related to dementia caused by misunderstanding. Many early

symptoms of AD, such as forgetfulness and agitation, have been attributed to normal aging. At the same time, genetic mutations and pathological changes in cells may have happened years before the first symptom. Thus, most people with AD miss the best time to delay its progression and do not pay attention until it is too late [8].

Recently, significant advancements have been made in the use of telemedicine in health care. Telemedicine is defined as the delivery of health care from a distance using electronic information and technology, such as computers and videoconferencing [9]. By administering cognitive assessments, such as the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) tests [10], online instead of the traditional in-person approach, early diagnosis is facilitated, allowing early monitoring and treatment. Further, telemedicine may also enable individuals who may not have easy access to a specialist for screening and check-ups, emphasizing the utility of expanding this service. Telemedicine has been shown to improve the quality of care for patients in terms of effectiveness, safety, people-centeredness, timeliness, equitability, integrated care, and efficiency [11].

The present article will discuss contemporary literature regarding recent advances in AD research. Specifically, this work will cover AD clinical manifestation, diagnosis, and mainstream hypothesis of pathophysiology. It will also explore frontiers in AD research, such as the role of microglia and Notch receptors, and discuss future treatment directions like music therapy and the use of telemedicine in AD diagnosis, monitoring, and treatment.

Methods

This literature review uses Google Scholar and PubMed as the primary databases. Most articles included are from the past 10 years (i.e. 2014-2023), with some articles from the last century (i.e. 1984-2000) to remind readers of how scientists' understanding of AD gradually unfolds. This review not only examines original research and review, but also includes seminar manuscripts. The initial search yielded over 200 relevant articles, and exclusion criteria includes outdated conclusions, lack of peer-reviewed status, limited cites, flawed methodological designs, etc. After in-depth analysis of the remained 76 articles, 63 articles are included in this review. Data extraction is based on the article's focus. Each article reviewed is categorized into themes (i.e. clinical manifestation, pathophysiology, treatment approach, etc.), and only relevant data and conclusions are extracted. Data and key findings from included studies are horizontally compared to results gained from similar studies to ensure accuracy and credibility.

Inclusion and Exclusion Criterion

Studies on subjects related to the use of telemedicine on AD, risk factors and pathophysiology of AD, and current diagnostic methods and treatments are included. Other subtypes of dementia (e.g. Parkinson's Disease) and prevention of AD are excluded. The effectiveness of telemedicine on AD diagnosis, treatment, and monitoring, and its risks and implications are especially included. All study designs (e.g. case-control accuracy study, paired comparative accuracy study, etc.) are included. Controversial literature, protocols, correspondence, commentaries, and opinions are excluded. Articles published in non-English language are excluded. Articles published later than June, 2024 are excluded.

Clinical Manifestations and Risk Factors

Clinical Manifestations

AD can be diagnosed, and distinguished from other forms of dementia, using a variety of diagnostic tests and criteria. Two commonly used diagnostic criteria for AD in both clinical and research settings are Braak's criterion (considers the entire brain) and CERAD criterion (focuses on the neocortex) [12]. Using Braak's criterion, patients are classified into five different stages based on the location of neurofibrillary tangles (NFTs)—first the transentorhinal area (Stage I), entorhinal region (Stage II), hippocampus proper (Stage III and IV), neocortex (Stage V), and finally primary cortex (V). The usefulness of this staging technique has been questioned because most patients are diagnosed with the final stage [13]. Using the CERAD criterion, the maximum density of neuritic plaques per 100X light microscopic field is calculated: stage A, less than 2 plaques; stage B, about 6; and stage C, more than 30. AD is diagnosed in patients younger than 50 with stage A, patients younger than 75 with stage B, and patients older than 75 with stage C. National Institute for Aging and Ronald and Nancy Reagan Institute of the Alzheimer's Association (NIA-RIA) criterion combines Braak's and CERAD staging, serving as a great predictor for AD with high specificity and moderate sensitivity. It is a standardized protocol in which the patient's age and clinical symptoms of dementia need to be incorporated, so CERAD is best used in a face-to-face, in person setting. In some cases, the NIA-RIA criterion incorporates the Thal Aβ scoring system, rather than CERAD system, in addition to Braak's criterion. Since the Thal Aβ scoring system evaluates all Aβ plaques regardless of their morphology, it is a better predictor of general dementia (sensitivity of 94% specificity 87.7%), rather than AD [10]. Clinicians may opt for CERAD scoring system if the cause of dementia needs to be determined, while Thal Aβ scoring system allows them distinct dementia and normal aging.

According to the 2011 National Institute on Aging and

Alzheimer's Association (NIA-AA), AD is recognized as a decline in language, visuospatial, and executive function[14]. Clinical stages for AD involve mild (early), moderate, and severe (last); in mild stage, patients may have difficulty recalling recent memories or have language disturbances; in moderate stage, patients may experience neuropsychiatric changes such as depression and irritability; in severe stage, patients lose the ability to manage environment and movement. Clinical symptoms may also involve impairment in visuospatial tasks and motor dysfunction[15].

AD can be classified broadly into two major categories: sporadic AD and familial AD. Sporadic AD is associated with a later onset than familial AD and is thought to be caused by complex interactions between an individual's environment and genetics. Familial AD (FAD) is caused by a specific genetic mutation that is passed on throughout families and is associated with a younger age of onset[16].

Pathophysiology

Pathophysiology is the functional changes that accompany a particular syndrome or disease[25]. There is no single conclusive answer to the underlying causes of AD. Some of the current hypotheses explaining the symptoms of AD include the amyloid cascade hypothesis, tau tangles, acetylcholine deficiency, and microglial activation. In this review, we will mainly focus on amyloid plaques, NFTs, neuroinflammation, and neurodegeneration[17,26,27].

Amyloid Cascade Hypothesis

The amyloid cascade hypothesis is one of the most prominent theories on the cause of AD. It claims that the abnormal accumulation of Amyloid Beta protein into plaques is the causative factor of neurodegeneration in AD[17]. Amyloid Beta is the main component of neuritic plaques, which may bind to different receptors and cause neuronal death. Therefore, understanding Aβ pathology is important to develop future treatments. Aβ, a 4-kDa peptide cleaved from a transmembrane protein called Amyloid Precursor Protein (APP) by γ-secretase, has two isoforms of Aβ40 and Aβ42. APP is a type 1 membrane glycoprotein involved in neuronal development and intracellular transportation. It can be cleaved in two different ways: amyloidogenic and non-amyloidogenic. The two isoforms are the products of the amyloidogenic process, in which APP is cleaved by β-secretase and γ-secretase to produce sAPPβ and Aβ, respectively[28]. In the non-amyloidogenic process, APP goes through α-secretase cleavage at the N-terminus, releasing sAPPα[29]. The membrane-tethered αCTF is then cut by γ-secretase to generate P3[30]. Although it is so-called "non-amyloidogenic", by no means should we overlook its pathological role in AD: P3 aggregates into oligomers and fibrils at an enhanced rate[31]. Aβ monomers aggregate to form Aβ oligomers as a result of the hydrophobic interactions and hydrogen bondings between amino acids. Aβ oligomers form a hexagonal shape; their high solubility means they can spread throughout the brain. Aβ oligomers can be further assembled into large, insoluble fibrils which contain β-strand segments. Fibrils are mostly insoluble, so they are responsible for binding to different receptors and blocking neuronal signaling[17].

Tau Hypothesis

Another well-established hypothesis is the tau hypothesis, which postulates the neurotoxicity of tau aggregation into paired helical filaments (PHFs) and NFTs[32]. Tau is a microtubule-associated protein commonly found in the intracellular domain of neurons. Encoded by gene MAPT on Chr 17q21, mutations in the splicing of exons 2, 3, and 10 result in six tau isoforms, all with three (3R) or four (4R) microtubule-binding repeat domains. With an extra R2 repeat domain, the 4R isoform of tau protein demonstrates a higher affinity to microtubules, thereby reducing its chances for aggregation[33]. Tau mainly consists of two domains whose borderline is the proline-rich area – the projection domain and the microtubule assembly domain. The projection domain projects away when tau binds to microtubules; the microtubule assembly domain contains the binding sites. Its hydrophilic and basic characteristics make it intrinsically unfolded in neurons and show little propensity for detaching microtubules[26].

Physiological functions of tau not only include the assembly of microtubules, but also regulate axonal transport by modulating the functions of motor proteins like kinesin and dynein. Post-translational modifications of tau play an important role in its pathophysiology[34]. Scientists widely believe that phosphorylated tau (eight phosphates per molecule) is pathological, and a study conducted on a normal post-mortem brain showed that phosphorylated tau appears at the same sites as those in AD brains, confirming that hyperphosphorylation is pathogenic. Hyperphosphorylated tau causes tau aggregation by reducing its affinity to microtubules, to which extent largely depends on the sites phosphates bind to. For example, the binding at the repeat domain and Ser214 leads to microtubule detachment, while the binding at Threonine-Proline hardly affects it.

Hyperphosphorylation causes neurodegeneration through other mechanisms as well: synaptic dysfunction resulting from tau missorting, altered degradation process by interfering with protease cleavage, and pathology-induced interactions with other biomolecules[26].

Neuroinflammation Hypothesis

A final hypothesis about the causes of the neuropathology of AD is that inflammation in the nervous system may lead to different symptoms. Although inflammation might seem quite far away

Risk Factors	Categories	Mechanisms	Risk
Genetics	Causative genes	APOE4 is a less effective variant of the APOE gene that hinders Aβ breakdown and lipid metabolism; mutations in PSEN1, PSEN2 genes lead to abnormal processing of APP, increasing expression of Aβ42; mutations in APP gene cause the resulting Aβ to be more prone to aggregate[17].	One allele of APOE4 increases the risk of AD by 3 to 7 times; two alleles of APOE4 increase the risk by 8 to 15 folds[18]. Mutations in PSEN1 gene account for 70% of early-onset familial AD cases; mutations in PSEN2 gene account for 5%; mutations in APP gene account for 15%[18].
	Protective genes	APOE2, PLCG2, KLOTHO[19]	
Lifestyle	Alcohol and Smoking	Alcohol and smoking exacerbate neuroinflammation and stimulate mutations.	Age of onset for heavy drinkers (over two drinks per day): 71.5 Non-drinkers: 75.6 Heavy smokers (over one pack per day): 73.2 Non-smokers: 75.7[20]
	Sleep	Sleep deprivation contributes to an increased risk of AD mainly through four mechanisms: the glymphatic clearance pathway, APOE delivery at the blood-brain barrier, increased synaptic activity, and neuroinflammation[21].	Rodent studies showed that the accumulation of Aβ during the day would be cleared at night, and forced wakefulness resulted in an abnormal increase in Aβ levels compared to baseline levels[22]. Cho's study in 2021 showed that female flight attendants who worked on transmeridian routes usually had a reduction in temporal lobe volume compared to those who worked on short routes[21].
Demographics	Age	Increase in neuritic plaques, accumulation of Aβ over years[23].	65-74: 5% 75-84: 13.2% 85+: 33.4%[23]
	Gender	Women have higher tau load than men[19].	Women are twice as likely to get AD as men[19].
Other factors	Covid-19	SARS-CoV-2, the pathogen that causes COVID-19, is a neurotropic and neuroinvasive virus. ACE-2 expression is not only found in the lungs but also in neurons and glial cells in the hippocampus and temporal lobe. It is hypothesized that SARS-CoV-2 exacerbates those predisposed to AD through immune activation or direct neurotoxicity, with some studies indicating that COVID-19 may even induce AD in older individuals[24].	In a cohort study of about 6 million elderly adults, COVID-19 significantly increases the risks of Alzheimer's Disease with a hazard ratio of 1.69, 95%[24].

Table 1 Risk Factors for Alzheimer's Disease

from the pathogenesis of AD, it actually contributes to neuronal death and exacerbates Aβ accumulation[35]. Neuroinflammation leads to AD through microglial activation. Microglia, commonly found in the parenchyma of the central nervous system, are resident immune phagocytes that constantly search for pathogens to start an immune response[36]. They also provide factors to maintain tissue integrity and neuronal plasticity. When a microglial activation is triggered by Aβ fibrils and neuritic plaques through cell-surface receptors such as CD36, CD14, CD47, and Toll-like receptors (TLR4, TLR6, and TLR9), it will migrate to the lesion and initiate innate immune response, in which chemokines and cytokines including TNFα, interleukin 1, interleukin 6, and interleukin 12 are released[37]. However, cytokine production is detected to be reduced with a genetic deletion in CD36, TLR4, or TLR6. Receptors that identify the danger-associated molecular patterns are involved in this proinflammatory process. After activation, microglia phagocytose insoluble Aβ fibrils which will be degraded by various enzymes like proteases neprilysin and insulin-degrading enzyme. In contrast, soluble Aβ oligomers can be degraded by extracellular protease without entering microglia[27].

Section Summary

As outlined in this paper, multiple hypotheses exist about the mechanisms underlying the development of AD. Overall, the Amyloid Cascade Hypothesis examines how an abnormal accumulation of Aβ caused by pathological cleavage of APP and its misfolding block vital signaling pathways in the brain; the Tau Hypothesis focuses on the mechanism of tau-phosphorylation leads to the disassembly of microtubules, causing neurons breakdown intracellularly. Some researchers believe that these two hypotheses are interrelated with each other; in other words, Aβ deposits exacerbate the process of tau hyperphosphorylation, while tau protein mediates Aβ toxicity. The Neuroinflammation Hypothesis parallels the first two hypotheses because insoluble Aβ and misfolding tau serve as the antigens activating a chronic immune response by triggering the release of cytokines and chemokines, which then accelerates Aβ and tau accumulation. This underscores the uncertainty that researchers and patients still face when dealing with AD and emphasizes the need to explore emerging technology and research frontiers.

Diagnosis and Assessment

AD is often diagnosed in late stages with the presence of severe clinical manifestations like deteriorating cognitive skills. The actual onset of AD, involving Aβ accumulation and chronic neuroinflammation, can be traced back ten to fifteen years before the first symptom[38]. Before 2000, AD diagnosis largely relied on clinical assessments[39]. Common clinical diagnostic tests include MMSE, the Hachiniski Ischemic Scale, the Dementia Rating Scale, and ADAS-cog test[40]. The MMSE uses 30 questions to quantitatively measure cognitive status including areas like time orientation, spatial orientation, recall, etc. A score of 24 or less corresponds to dementia, with lower scores indicating more severe dementia. With a sensitivity and specificity of 79.8% and 81.3%, the test takes 10 to 15 minutes to complete. The ADAS-cog test measures six areas of cognition – memory, language, orientation, planning, etc. A higher score indicates a greater cognitive impairment. With a sensitivity and specificity of 89.19% and 88.53%, the administration time is about 30 to 45 minutes[10]. In 1989, Wolf-Klein et al. called for a valid and easily administered screening procedure: Clock Drawing41. Clock Drawing Test has been proven to be a low-cost, effective screening procedure for AD. A Jewish Institute for Geriatric Care identified 10 clock patterns, which include irrelevant figure, irrelevant spatial arrangement, other, counterclockwise rotation, absence of number, preservation, very inappropriate spacing, almost normal except for spacing, almost normal except for number, and normal, associated with different mental status – normal mental status, Alzheimer's Disease, multi-infarct dementia (MID), combined AD and MID. The first six clock patterns are widely believed to be AD-related, while the rest are considered normal. The clock patterns were tested for specificity, sensitivity, and correct identification. As a test for AD, Clock Drawing has a high specificity of 94.2%, while a low sensitivity of 75.2%. This is probably caused by the fact that Clock Drawing depends on spatial orientation, and thus only reflects patients with temporoparietal involvement[41].

Treatment Approach

The use of telemedicine

Telemedicine is defined as the remote diagnosis and treatments of patients using information and communication technology. Synchronous, Asynchronous, and remote monitoring make up the three main types of telemedicine. Synchronous monitoring involves real-time interactions between patients and caregivers; asynchronous monitoring refers to the transfer of prerecorded neuroimaging data to the physicians; remote monitoring is the continuous assessments of patients' conditions through videoconferencing[10]. Telemedicine can be performed in various ways and for different purposes. The most used diagnostic technology is videoconferencing. The others include virtual reality on a touch screen, motion and contact sensors, interactive voice response, and display for cognitive tests administration[45]. Videoconferencing and display for cognitive tests can be used for diagnosis. Motion and contact sensors involve in daily injury prevention and help patients navigate safely in their everyday environment. Interactive voice response and virtual reality serve as media for cognitive rehabilitation exercises and medication

	Type	Drug(s) / Method	Mechanism	Effectiveness
Current medications	Acetylcholinesterase-inhibitors (ChEIs)	Donepezil, Tacrine, Galantamine	Acetylcholinesterase binds to presenilin-1 and increases extracellular Aβ levels; acetylcholine (an important neurotransmitter) is also rapidly broken down by acetylcholinesterase. ChEIs inhibit the enzyme's activity[42].	Current FDA-approved drugs only show temporary symptomatic relief.
	N-methyl-D-aspartate antagonists	Memantine	Memantine works as the antagonist of glutamate receptors to prevent the overactivation of neurons caused by the excitatory effect of the neurotransmitter, which may lead to neurotoxicity[43].	
Non-pharmacological interventions	Music therapy	Music therapy should be tailored to meet each individual's music preference and carried out in groups to maximize its effectiveness. The music therapy sessions were held twice weekly for 45 minutes and lasted 6 weeks in total[44].	Music, as a pleasant stimulus, decreases the activation of the parasympathetic nervous system, which triggers aggressiveness. It improves cognitive function by engaging the right hemisphere and temporal lobe, enhancing speech processing, memory retention, and emotional recognition[44].	A study by Gallego and Carcia (2017) on 42 geriatric patients (27 women; mean age 77.5 ± 8.3 years) demonstrated that music therapy improves both neuropsychiatric symptoms and cognitive skills in AD patients[44].

Table 2 Existing treatment approaches

compliance monitoring.

Telemedicine holds a promising future in AD diagnosis, monitoring, and treatment. The benefits of telemedicine include easy accessibility, lower cost, and decreased workload for caregivers; however, limitations include the requirement for certain technology literacy, data security, and the quality of data transmission. Ethical and legal aspects of telemedicine are worth considering as well: the problem of informed consent, duty to maintain confidentiality, and privacy of medical records post obstacles against telemedicine implementation. In 2018, Carotenuto et al. conducted a pilot study evaluating the reliability of MMSE and ADAS-cog tests in hospital through videoconferencing. The study showed no difference in diagnostic results when tests were administered online and in person, except for patients with severe dementia at enrollment, in which the assessment tends to overestimate the cognitive impairment. According to the telemedicine acceptance survey, completed by a short questionnaire after the examination, 98% of patients and caregivers had a positive experience with this modality. Since this pilot study was conducted on only 28 AD outpatients in a hospital, the inclusion of a larger sample and a different setting should be considered in future studies[10]. However, subsequent studies with larger sample sizes conducted by Cullum et al. (202 participants), Lindauer et al. (66 participants), and Lott et al. (90 participants) all show perfect corresponding of test scores in online and in-person settings[46–48]. Therefore, the overestimation in AD diagnosis in Carotenuto's study may be caused by the small, less diverse sample.

Emerging Technologies and Research Frontiers

Innovative Treatment Approach

Current treatments for AD remain uncompleted or unsatisfying: drugs like memantine, acetylcholinesterase inhibitor, and donepezil often arouse safety concerns and fail to disease development for long. This is where stem cell technologies come into play. Since 2006, when a Japanese stem cell researcher Shinya Yamanaka, and colleagues first generated induced pluripotent stem cell (iPSCs), this technology has been used for drug screening and cell therapy. In the past several years, scientists unlocked more potential of stem cell technology, including the creation of repositories of iPSCs from AD patients, a better understanding of Aβ and tau theories, and transplantation of mutation-free stem cells with the help of gene-editing techniques. Neuronal subtypes such as microglia and some forebrain neurons can now be regenerated. Specifically, microglia is under the spotlight as a potential therapeutic agent because about 8 genes associated with AD are densely expressed in microglia. Somatic cells are retrieved from AD patients and reprogrammed into patient-specific iPSCs (eg. embryonic interneuron progenitors) by activating four transcription factors (i.e. Oct4, Sox2, Klf4, and c-Myc). Subsequently, mutations in the iPSCs will be corrected. After transplantation in the CNS, mutation-free neurons or microglia will gradually replace pathogenic ones, thereby alleviating the problem. Stem cell therapy is relatively safer reprogrammed cells exhibit a lower risk of cancer. However, problems and concerns still exist. First, the success of stem cell transplantation is only seen in animal models, and there is a likelihood that it may not be able to restore neuron circuits to their normal states. In other words, the function of stem cell therapy is by no means different from the other treatments, which have limited efficacy. Second, creating patient-specific iPSCs can be expensive and time-consuming, not to mention the ethical problems it may intrigue. Last, there are more questions involved in stem cell therapy that need to be solved. For example, would factors such as disease stage and phenotype influence the cell types to be chosen for iPSC? Another aspect of stem cell technology is related to drug screening. Using an iPSC-based model in vitro, Liu and colleagues discovered that the dosing of semagacestat, a drug for AD treatment, should be lowered compared to the dosage used in a transgenic mouse model[32]. In a study focusing on the different effects of APOE4 and APOE3 in sAD patient-derived stem cells, Wang C and colleagues found that Aβ concentration has no direct influence on p-tau levels, suggesting a distinct pathway that causes tau phosphorylation[26].

Effectiveness and Future of Telemedicine

According to another systematic review of 56 articles by Costanzo et al., the use of telemedicine is effective in helping improve early diagnosis, supporting patients' memory and orientation problems, and supporting caregivers. Specifically, the accuracy and efficacy of telemedicine diagnosis is almost the same as in-person diagnosis, except in one article in which the authors found an overestimation of cognitive impairment in telemedicine diagnosis. Telemedicine also improves the overall experience of patients' follow-up for both patients and caregivers. For patients, the use of reminiscent music and verbal cues helps of recapture past memories and basic activities. The use of basic orientation technology such as a night monitoring system drastically reduces the relative risk of injuries by 86%. The night monitoring system is especially important for AD patients because it takes on the role of a caregivers when their care is absent during night time. Tele-assistance wearable, another home-based injury-prevention technology, is also shown to significantly reduce the risk of indoors falling (32.7% of falling accidents in the intervention group versus 63.8% in the control group). In addition, Smith et al tested the acceptability and effectiveness of installing a tele-video monitoring equipment in one group of patients' houses to monitor their medication compliance. They found that the accuracy of self-administration and patients' mood is significantly improved compared to groups with only audio monitoring and no monitoring at all. Some other internet-based technologies aim at alleviating clinical symptoms through cognitive stimulation and rehabilitation. For example, a psychostimulation program, designed to stimulate the effects of cholinerase inhibitors, involves 12 weeks of intensive training in different domains of the brain including attention, recall, calculation, etc. Although the group only treated with cholinerase inhibitors and group received both the program and cholinerase inhibitors both showed increased ADAS-cog score, only the latter group has an extended effect over 24 weeks. For caregivers, telemedicine is often rated in a positive way. In an Australian trial study involving 18 caregivers, they not only recognized productive interactions can be achieved in both online and in-person meeting, but also they found videoconferencing reducing stress, emotional burden, and decreasing perceived social isolation[45].

Telemedicine provides the chance to transform Alzheimer's disease care by enhancing accessibility, personalization, and support for patients and caregivers. With ongoing technological advancements, the role of telemedicine in this field is expected to expand exponentially. AD diagnosis is highly resource-dependent, which can be attributed to the following reasons: availability of local hospitals or health-specialists, accessibility of cognitive testings, and the lack of awareness and patient-compliance. Telemedicine allows patients and caregivers to overcome geographical barriers and mobility issues because cognitive assessments and screenings can be administered online via video-conferencing tools like Zoom. Early detection of AD can be easily achieved if AD screening becomes highly accessible, especially for the disabled and people living rural areas. Telemedicine also helps with disease management including routine monitoring and medication management. Specifically,

without the need for physical travel or in-person appointments, patients can have regular follow-ups with doctors at any location. Thanks to the progress of digital health, apps that monitor subtle changes in behavior, sleep patterns, and other parameters appear, making the monitoring process simpler and more accurate. Caregivers can adjust treatment approach, and medication dosage, and manage side effects based on patients' daily behaviors in the setting they are the most familiar with. Moreover, research done on 259 in-person patients and 168 telemedicine patients reveals that telemedicine is associated with longer treatment duration and patients' compliance in a 5-year period[49]. Through videoconferencing, health specialists can train family members how to take care of patients, which includes reminding patients to take medications, giving them emotional support, and aiding their physical activities. Last but not least, telemedicine opens the possibility of holding music therapy sessions online. Without the need of living in an assisted-living facility, patients can not only benefit from the therapeutic effects of music itself, but also engage in conversations with people from all around the globe at the lowest expense possible.

Conclusions and implications

AD is one of the most devastating brain disorders for the elderly and their families, which causes memory loss and cognitive disabilities severe enough to interfere with their daily lives. Early diagnosis of AD is difficult because mild symptoms like forgetfulness are often dismissed as a part of normal aging. Effective treatments for AD remain limited and there is no definite cure for it because of our incomplete understanding of the pathophysiology underlying AD. People should recognize that there is no one exclusive cause of AD; rather, all current etiological hypotheses are interrelated. However, progress in AD research in the past few decades is evident, as advanced neuroimaging techniques and innovative therapeutics are being developed. Future research directions include early diagnosis and better treatments of AD. The development of PET-scan tracers with higher binding specificity to their targets plays an important role in enhancing current neuroimaging techniques. The use of stem cells gives new insights into comprehending AD pathology, and it offers the possibility of treating AD at a genetic level by creating mutation-free neurons. Stem cell therapy is highly specific to each individual, so an iPSCs repository should be established to promote its application. Nanodrug delivery system should be more extensively explored as its ability to deliver drugs effectively into the central nervous system makes it a strong candidate for potential AD cure. Finally, telemedicine brings AD diagnosis, treatment, and disease monitoring online, making AD intervention a convenient process rather than an unimaginable burden.

Challenges and Implications of Telemedicine

Even though telemedicine provides a great chance for AD early diagnosis, longer treatment duration, and easier disease monitoring, it still faces numerous challenges that hampers its adoption universally. According to a systematic review of 27 studies by Ftouni et al., technical barriers, privacy and data conditionality, and physical examination are three most significant problems that need to be addressed. 21 out of 27 studies report technical issues as one of the major difficulties of implementing telemedicine. In some developing countries and rural areas of some developed countries, there is no stable internet access, high resolution camera, or a connection in sync enough to ensure a smooth conversation. Some patients have trouble using a smartphone and navigating different videoconference platforms. The other problem concerns data security. More than half of the studies mention patients' worry of private information being shared with a third-party. Patients' concerns can be alleviated to some extend by healthcare providers obtaining informed consent from patients, or signing a contract with patients that ensures complete confidentiality. Lastly, due to the nature of physical examination, it simply cannot be performed online. In this case, patients using telemedicine will have trouble updating their conditions and getting time-sensitive feedback from their physicians[50].

Abbreviation Table

Abbreviation	Corresponding Word(s)
AD	Alzheimer's Disease
CERAD	Consortium to Establish a Registry for Alzheimer's Disease criterion
MMSE	Mini-Mental State Examination
ADAS-cog	The Alzheimer's Disease Assessment Scale cognitive subscale tests
NFTs	Neurofibrillary tangles
NIA-RIA	National Institute for Aging and Ronald and Nancy Reagan Institute of the Alzheimer's Association criterion
FAD	Familial AD
APP	Amyloid Precursor Protein
PHFs	Paired helical filaments
MID	Multi-infarct dementia
ChEIs	Acetylcholinesterase-inhibitors

Table 3 Abbreviations

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