

Digital Therapeutics in the Application of Alzheimer's Disease

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Abstract. As the global population continues to age, the prevalence of Alzheimer's disease (AD) escalates, placing a significant strain on healthcare systems worldwide. While diagnostic methods and therapeutic drugs for AD remain in development, digital therapy emerges as a novel non-pharmacological treatment or adjunctive measure, offering a promising avenue for the diagnosis, prevention, treatment, and management of AD. This article provides an overview of digital therapeutics (DTx) applications, encompassing cognitive assessment, intervention, and risk management, with the intent of informing clinical practice in AD. DTx employs software-driven interventions, such as cognitive training and virtual reality, customized to address patient needs, thereby furnishing real-time assistance to caregivers and patients alike. However, despite its potential, DTx encounters challenges regarding evidence consistency and integration into existing healthcare frameworks. Future research endeavors should prioritize robust experimental designs and interdisciplinary collaborations to enhance the efficacy and accessibility of DTx. Policymakers and healthcare providers must consider the integration and training of DTx to fully harness their benefits in AD management. This study underscores the pivotal role of DTx in shaping the future of AD care and emphasizes the necessity for concerted collaborative efforts across research, policy, and practice domains.

Keywords: Digital therapeutics, Alzheimer's disease, Application.

1. Introduction

Amidst the global phenomenon of population aging, the prevalence of dementia among older individuals continues to rise steadily, with projections estimating a surge to 152 million cases by the year 2050 [1]. Dementia has emerged as a significant contributor to mortality and disability among the elderly, with Alzheimer's disease (AD) standing out as the primary culprit. AD is characterized by progressive cognitive decline and behavioral disturbances, imposing a substantial social and economic burden. Mild cognitive impairment (MCI) acts as a transitional phase between typical cognitive abilities and onset of AD dementia, often progressing to AD dementia with a high probability [2]. Hence, fostering early detection and intervention, particularly during the MCI phase, holds promise in either preventing or delaying the onset and progression of AD, thereby contributing significantly to promoting healthy aging. Although some pharmaceutical and non-pharmaceutical treatments exist to alleviate AD symptoms, their efficacy remains limited and often accompanied by adverse effects. There exists an urgent imperative to discover more effective and safer treatment modalities.

Digital therapeutics (DTx), as an innovative non-pharmacological intervention or adjunct, offers an effective supplementary approach for the diagnosis, prevention, treatment, and management of AD. DTx refers to software-driven, evidence-based intervention schemes aimed at preventing, treating, or managing diseases and improving disease prognosis [3]. It can be utilized independently or in conjunction with pharmaceuticals and other non-pharmacological treatments. DTx encompasses three primary categories, each serving a distinct purpose in healthcare. The first category is prevention: this involves the deployment of digital interventions to individuals who may be asymptomatic but harbor certain risk factors that predispose them to future illnesses. By leveraging these interventions, the onset of diseases can be mitigated or delayed. The second category pertains to treatment: following a formal diagnosis, patients are furnished with digital intervention methodologies that aim to eradicate the disease and reinstate health, guided by specific medical protocols, clinical directives, or established gold-standard therapies. Lastly, the third category is management: post-diagnosis,

patients are educated and supported in self-managing their condition along with the various elements that could exacerbate the progression of the disease. Through this approach, digital intervention methods are utilized to control the disease's trajectory, minimize potential complications, or alleviate adverse side effects. DTx typically encompasses three key elements: (1) it must be software-driven; (2) grounded in evidence-based medicine and guided by healthcare professionals; (3) subject to approval and oversight by relevant regulatory authorities.

As a novel adjunctive treatment modality, DTx boasts several advantages [4]. Firstly, it offers convenience and flexibility. Patients can access treatment anytime, anywhere through smartphones or tablets, transcending constraints of time and location, thereby enhancing the efficiency of disease diagnosis and treatment and bolstering patient accessibility. Secondly, it enables personalized treatment. Leveraging intelligent algorithms and big data analysis, DTx can tailor treatment plans according to individual patient characteristics and disease progression, thereby optimizing treatment specificity and effectiveness, and ultimately enhancing treatment outcomes. Thirdly, it entails lower costs and risks. In comparison to traditional drug therapies and rehabilitative interventions, DTx typically incurs lower costs and is associated with fewer serious side effects, consequently alleviating the economic burden and safety risks associated with treatment. DTx aligns seamlessly with the rapid advancements of the information age and holds immense potential for further development. Therefore, this article endeavors to elucidate the progress of DTx applications in the prevention and treatment of AD, exploring and assessing issues such as digital cognitive assessment, cognitive interventions, and risk management. The aim is to furnish insights for the clinical diagnosis and treatment of AD.

2. Clinical Application and Efficacy of Dtx in AD

2.1. Cognitive Assessment

DTx-based cognitive assessment encompasses various approaches, including computerized scale-based assessments, widely used electronic systems for neuropsychological evaluations, and computerized task-based assessments. Certain digital cognitive assessment tools have demonstrated strong consistency with traditional paper-based assessments and heightened sensitivity, thus holding promising prospects for broad applications [5].

The US Preventive Services Task Force recommends cognitive screening for suspected MCI patients. Computerized cognitive tests commonly employ list-learning paradigms and paired-association learning paradigms for MCI screening. These tests offer the advantage of continuously recalling the target information across repeated trials, enabling sensitive identification of retrieval deficits while also facilitating maximal information storage for subsequent comparison with delayed recall results. Revere software serves as a digital version of the verbal contextual memory test, operates on tablets for self-administration and automatic scoring of word list tests. Research findings indicate comparable verbal memory performance between participants utilizing Revere and those undergoing RAVLT assessments [6].

Furthermore, digital cognitive assessment can efficiently and comprehensively evaluate patients' overall cognitive function, specific cognitive domains, social and daily living abilities, and mental behavioral symptoms by integrating virtual reality, specialized speech recognition devices, eye-tracking, and other cutting-edge technologies. For instance, utilizing virtual reality technology to construct a simulated supermarket scenario, where participants completed shopping tasks using interactive devices. Variables recorded during the shopping process exhibited a high correlation with results from traditional neuropsychological tests. Remarkably, the virtual supermarket achieved an impressive 81% accuracy rate in distinguishing between individuals with MCI and healthy counterparts. Additionally, a moderate correlation between eye-tracking-based cognitive assessment tasks, such as visual comparison tasks, and traditional cognitive assessments, indicating its potential for detecting early cognitive changes.

These assessment techniques can be seamlessly integrated through platform interfaces developed during computer programming, enabling effective fusion of multimodal data. This facilitates a

comprehensive and dynamic evaluation of AD symptoms, establishing a closed loop of data transmission synchronized with the intervention process. Implementation of digital cognitive assessment not only allows for a flexible combination of assessment content and rapid result output but also addresses the demand for large-scale cognitive function screening across diverse medical settings, including hospitals, communities, and nursing homes.

2.2. Cognitive Intervention

DTx-based cognitive interventions encompass computerized cognitive training, virtual reality, and neurostimulation techniques. Diverging from traditional cognitive interventions, digital cognitive interventions target impaired cognitive functions through computer systems or employ wearable devices, virtual reality technology, and physical stimuli to achieve comprehensive training across multiple cognitive domains. Continuous monitoring of training via the internet, real-time feedback data analysis, dynamic adjustment of training dosage, and ongoing monitoring of process and effects bolster participant confidence and compliance with the intervention [7].

Digital cognitive intervention effectively prevents and treats cognitive decline, facilitating cross-disease, multi-domain, and multi-modal interventions. It enhances key cognitive domains and overall cognitive function in individuals with cognitive impairment diseases, with intervention measures being utilized alone or in combination. A study examining effectiveness of digital cognitive training in elderly individuals with MCI or dementia revealed significant associations with improved cognitive performance, daily life activity ability, and reduction in neuropsychiatric symptoms [8]. Furthermore, computerized cognitive training targeting multiple cognitive domains can enhance overall cognitive function and specific cognitive subdomains in patients with cognitive impairment [8]. Notably, computerized cognitive training garners high feasibility and acceptability among participants. Furthermore, neurostimulation methods show encouraging outcomes in markedly enhancing the cognitive function of target population [9]. Optimization of parameter adjustments yields stronger cognitive enhancement effects, particularly enhancing memory, and overall cognitive function in AD patients [9].

Moreover, digital cognitive intervention is progressively finding its application within home environments, demonstrating promising efficacy. Tailored training programs enhance compliance, and home-based training supported by family members or partners significantly amplifies training effectiveness. Internet-based remote cognitive intervention markedly enhanced the overall cognitive function of individuals with AD, particularly in language, executive function, and memory domains. This approach also effectively bolstered treatment compliance among patients undergoing home-based interventions. Marin et al. implemented a 24-week home-based computerized cognitive training program tailored for individuals with MCI and mild AD [10]. Task difficulty levels were dynamically adjusted based on individual capabilities. The findings revealed noteworthy improvements in distinct cognitive areas such as visual and auditory memory, along with attention. Compared to traditional face-to-face cognitive interventions, a family-based, self-management-oriented approach to computerized cognitive intervention presents a pragmatic alternative, overcoming cost and persistence challenges associated with traditional supervised cognitive training programs.

2.3. Remote Real-Time Monitoring

DTx leveraging information communication technology, including sensors, global navigation satellite systems, cameras, and wearable devices, facilitates the real-time acquisition of objective and quantifiable physiological data from AD patients. Through analysis of daily physiological behavioral patterns, changes in cognitive function and daily living abilities can be closely monitored. The accuracy and effectiveness of smartphone apps, wearable devices, and home sensors in measuring functional decline from preclinical to moderate AD stages in real-world settings has been effectively demonstrated.

Moreover, early-stage AD and mild behavioral impairment often manifest as decreased motivation, emotional instability, impulse control disorders, and social discomfort, all of which heighten the risk

of AD progression. Research indicates that reduced activity correlates with the severity of apathy and sedentary behavior in AD patients, while increased activity is closely linked to the severity of agitation and the frequency of aggressive behavior [11]. Global navigation satellite system-acquired location information enables monitoring of wandering behavior in dementia patients, effectively preventing wandering incidents. Furthermore, a portable EEG device integrated into a self-help sleep monitoring-intervention system records and analyzes sleep feature waves and patterns. Coupled with targeted memory reactivation intervention measures, it facilitates tracking and prediction of treatment outcomes for patients [12]. As information technology continues to advance and its application expands, remote real-time monitoring will assume an increasingly pivotal role in AD treatment, furnishing more personalized and precise medical services for patients.

2.4. Daily Living Assistance

Through information communication devices, cognitive care auxiliary decision support systems, and other DTx, assistance for AD patients and their caregivers is readily accessible, facilitating daily activity management, enhancing patients' daily living abilities, and alleviating caregiving burdens. Personal digital assistant programs, including calendars and reminder alarms, aid patients in managing daily tasks and activities, mitigating the risk of forgetting or missing important matters. Decision support tools utilizing video, audio, and network-based technologies effectively assist caregivers of individuals with cognitive impairment in making informed care decisions [13]. Devices leveraging global navigation satellite systems have demonstrated efficacy in enhancing dementia patients' sense of security, thereby reducing fear and anxiety [14]. Moreover, the integration of a portable EEG device with a comprehensive physiological signal-assisted control-release drug delivery system and real-time feedback from data terminals facilitates timely medication interventions for patients. Upon detection of abnormal characteristic waves, this system administers subcutaneous implanted controlled-release medication, thereby enhancing patient compliance with medication interventions [15].

A study pioneered the advancement of digital reminiscence therapy (RT) utilizing digital technology, validating its efficacy through a randomized controlled trial involving dementia patients [16]. Digital RT offers a plethora of captivating multimedia resources. Unlike conventional RT techniques, these multimedia elements offer increased sensory stimulation, emotional support, and social interaction opportunities for participants, ultimately ameliorating depressive symptoms. In essence, DTx exerts significant effects in providing daily living assistance for AD patients, fostering independence, and enhancing the overall quality of life for patients.

3. Discussion

3.1. Potential Impacts of Dtx

AD, like other neurodegenerative conditions, progresses gradually over time, affecting both the clinical status of individuals and the dynamics of their family life, both of which are continually evolving. The essence of Digital Therapeutics (DTx) lies in utilizing software-driven interventions to prevent, manage, or treat diseases. In the context of AD, this often involves applications for cognitive training, virtual reality technologies, and AI-based personalized interventions. The effectiveness of these technologies is partly attributed to their capacity to provide standardized, yet individualized interventions tailored to the cognitive and functional levels of diverse patients. Furthermore, a significant yet understated aspect of DTx is their ability to offer real-time or near-real-time intervention opportunities, empowering caregivers, and sometimes even patients themselves, to better manage their care and activities of daily living. Through these technologies, stakeholders can make informed decisions and continuously monitor the progression of patients throughout the disease.

3.2. Challenges of DTx

Although DTx has been incorporated into the assessment, intervention, and management of AD, they confront numerous challenges in areas such as clinical validation research, technological usability, privacy and data security, policy oversight, and economic implications.

Emerging studies suggest promise in digital therapeutics for enhancing cognitive function and life quality in AD patients [11, 12]. However, the current body of evidence is inadequate to endorse their extensive application within clinical settings. Consensus from recent meta-analyses and systematic reviews underscores the paucity of high-quality evidence for the deployment of digital therapeutics within healthcare services. This situation can be attributed to several pivotal factors: (1) many clinical trials investigating digital therapeutics for cognitive disorders remain at the proof-of-concept stage, constrained by small cohorts and brief follow-up durations, which compromises the reliability and statistical robustness of the findings; (2) limitations in study design—such as the absence of control groups or suboptimal randomization—further contribute to this issue; (3) a thorough evaluation of the enduring effects of digital therapeutics is yet to be achieved. Rigorous study designs, augmented sample sizes, and extended observation periods may offer new insights into these preliminary significant findings. Furthermore, the employment of varied assessment tools and outcome measures across different studies results in challenges to the comparability of findings. Crucially, most trials have not delved into exploring the neurobiological mechanisms that potentially underlie the positive impacts of digital therapeutics, hindering a comprehensive grasp of their therapeutic efficacy and potential refinement [8].

The practical implementation of DTx in AD must also surmount technical and operational hurdles. A considerable portion of the elderly population exhibits limited receptiveness and proficiency with novel technologies and may encounter resistance in adapting to and utilizing such tools due to technophobia or cognitive decline. For seniors with little to no exposure to modern technology, the complexity of user interfaces poses a formidable barrier. Consequently, when integrating DTx into intervention strategies, it is essential to gauge the acceptance level among patients and their caregivers, as well as their competence in operating related software—such as assessing the willingness of elderly patients to embrace these burgeoning therapeutic options. In tandem, DTx necessitates the handling and storage of vast amounts of sensitive data, presenting risks to patient privacy and data integrity that are imperative to address. On another note, DTx requires authorization and ongoing supervision from pharmaceutical regulatory bodies, yet there exists a deficiency in a more developed regulatory framework for vetting DTx products. Under the regulatory framework for medical devices, clinical experts have divergent opinions on the clinical use (prescription/non-prescription) of digital therapeutic products, largely depending on the positioning of the products by the companies. Therefore, ensuring the appropriate application of digital therapeutic products in suitable populations, reducing risks, and optimizing the allocation of medical resources are significant challenges currently faced. Moreover, compared to conventional digital health solution providers, the research, development, and operational expenditures for DTx are significantly elevated.

3.3. Future Perspectives

In the future, the development of DTx should focus on several key areas. Firstly, DTx applied to AD must closely align with advancements in cognitive neuroscience research, grounded in evidence-based medicine, to provide a comprehensive suite of tools for prevention, assessment, diagnosis, treatment, and management for individuals with AD. Secondly, the clinical validation of DTx can incorporate objective measurement indices such as imaging, electrophysiology, and blood biomarkers, and undertake rigorous clinical study designs that target the causative factors of AD. Thirdly, the selection of DTx should aim to improve patients' quality of lives. The design of content and tasks should reflect daily living skills more accurately, providing patients with intelligent, personalized digital diagnostic and therapeutic services through artificial intelligence technology and wearable equipment. Fourthly, the implementation of DTx should comply with privacy and data security protection requirements, safeguarding user information through the establishment of data security

systems and protective measures. Lastly, regulatory bodies should establish dedicated regulatory channels based on the unique characteristics of DTx, formulating targeted regulatory policies for the clinical safety, efficacy, usage conditions, and classification of DTx products.

4. Conclusion

With the rapid development of information technology, DTx, as an emerging treatment modality, brings new hope to patients with AD. This study focuses on the application of DTx in AD, exploring its potential impact, current limitations, and future development directions. Future research efforts should aim to strengthen experimental design and provide more consistent and in-depth evidence to clarify the effectiveness and safety of DTx in AD treatment. Additionally, interdisciplinary collaboration, such as integrating knowledge from neuroscience, computer science, and behavioral psychology, will help develop more precise and efficient DTx solutions. At the same time, policymakers and healthcare providers need to consider how to integrate DTx into existing AD management systems, including how to train professionals to support patients in using these tools, and how to ensure coverage for these new therapies within the healthcare insurance system. And, this study underscores the pivotal role of DTx in shaping the future of AD care and emphasizes the necessity for concerted collaborative efforts across research, policy, and practice domains.

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