

Acupuncture therapy in the management of Alzheimer's disease: literaturereview

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Abstract

Alzheimer's Disease is the main cause of dementia and represents a growing issue for health care, so it is essential that professionals in the field are prepared to manage these patients properly. However, countless studies show that the most used pharmacological classes, as the cholinesterase inhibitors, present limited efficacy and safety, which implies that disease-modifying treatments remain unknown. Thus, new studies came up proposing the investigation of different therapeutic interventions, such as acupuncture, which presents itself as an emerging and innovative treatment, since the current findings point to its great potential for effectiveness, in addition to showing fewer associated adverse effects.

Keywords: Alzheimer 's Disease. Acupuncture. Alternative Therapy. Efficacy. Safety.

Terapia de Acupuntura no manejo da doença de Alzheimer: revisão de literatura

Resumo

A Doença de Alzheimer é a principal causa de demência e representa um problema de saúde crescente, de forma que é essencial que os profissionais da saúde estejam preparados para fazer o manejo adequado desses pacientes.



Entretanto, inúmeros estudos apontam que as classes farmacológicas mais utilizadas, como os inibidores da colinesterase, apresentam eficácia e segurança limitada, de modo que podemos afirmar que os tratamentos modificadores da doença permanecem desconhecidos. Assim, surgiram novos estudos que propõem a investigação de diferentes intervenções terapêuticas, tais como a acupuntura, que se apresenta como um tratamento emergente e inovador, visto que os achados atuais apontam que ela apresenta um grande potencial de eficácia, além de ter menos efeitos adversos associados.

Palavras-chave: Doença de Alzheimer. Acupuntura. Terapia Alternativa. Eficácia. Segurança.

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1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disease of uncertain cause that primarily affects individuals in older age and is the most common cause of dementia (BALLARD, 2011). Globally, about 47 million people were living with dementia in 2015, and this number is projected to triple by 2050, based on the World Alzheimer's Report (2015).

Memory impairment is the most common initial symptom of AD dementia. In patients with the typical form of the disease, deficits in other cognitive domains may appear with or after the development of memory impairment (APA, 2013). Although there are treatments available that may improve some symptoms of the disease, there is currently no cure for AD. The gold standard for assessing the progression of AD is scale-based, most notably those developed in North America from mental status scales such as the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the clinical dementia rating scale, in addition to the aid of neuroimaging instruments, biomarkers, and genetic testing (NGO; DORAISWAMY; LAD, 2018).

Acupuncture refers to a family of procedures used to stimulate anatomical points and originated in China about 2,000 years ago, being one of the oldest medical procedures in the world. And, as the review by Scheffold, Hsieh, and Litscher (2015) cites, several physiological models have been proposed to try to explain the effects of acupuncture, and have included cytokines, hormones (e.g., cortisol and oxytocin), biomechanical effects,



electromagnetic effects, involvement of the immune system, and the autonomic and somatic nervous systems in the mechanism of action.

Acupuncture has improved memory and cognitive impairment in clinical and experimental studies, and may be an effective treatment for AD (HUANG, 2019). Researchers on the subject suggest that acupuncture may protect neurons from deterioration and promote axonal growth in neurodegenerative diseases, such as AD (WANG, 2020). The present study aims to conduct a literature review on the possible use of acupuncture for the treatment of individuals with AD, compared to traditional treatments.

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2 Methodology

This study is a narrative review of the literature, conducted between October and December 2020, which aims to understand the role of acupuncture as a possible form of treatment for Alzheimer's disease. A search for scientific articles was conducted in the Medline and Cochrane reference databases. In addition, in an attempt to include national studies, the indexing base Summaries of Brazilian Journals (Sumários.org) was used; however, no article was found. For the database search the descriptors "acupuncture therapy and Alzheimer's" were used. The inclusion criteria were articles published in Portuguese or English language in the last five years and that addressed diagnosis of Alzheimer's disease, acupuncture therapy, pharmacological treatment and other non-pharmacological therapies for AD. Studies with subjects under 18 years of age and that were not available in full, with only the abstract, were excluded. Systematic reviews and meta-analyses were preferred, although literature reviews on the biochemical neurological mechanisms involved in acupuncture were included. The search resulted in 27 articles in the Cochrane database and 87 articles in the Medline database, totaling 114 articles, of which 28 were pre-selected by reading the title and abstract, and of these, eight were included in the review.

The synthesis of the studies has been presented in Table 1:

Author	Sample/Characteristic	Objective	Main results	Magazine
Wang et al., 2020	Systematic review and meta-analysis. Eight databases were used to identify relevant randomized clinical trials published up to January 19, 2019, so that 3,099 articles were found. Of these, 30 clinical trials were selected, adding up to a total of 2,045 patients.	To comprehensively search the literature, critically evaluate the quality of methodology, summarize and compare the efficacy and safety of acupuncture therapy administered for different time periods, in order to help advance the medical treatment of AD.	Acupuncture associated with drug therapy may have a more beneficial effect for AD patients than drug therapy alone on general cognitive function in the short to medium term and on activities of daily living in the medium term. However, acupuncture alone may not be superior to drug therapy. Further Clinical Trials Needed.	Frontiers in Aging Neuroscience
Jia et al., 2017	Randomized clinical trial. 87 participants were included, of these 43 received acupuncture treatment (AG) and 44 received treatment with donepezilla (GD).	To determine the efficacy and safety of acupuncture among patients with mild to moderate AD.	Acupuncture is well tolerated and can improve cognitive function and overall clinical status. But its effect appeared to be limited and it was not possible to determine whether it is safer than donepezil, due to the small sample size.	BMC Complementary and Alternative Medicine
Huang et al., 2019	Systematic review and meta-analysis of randomized clinical trials on acupuncture for the treatment of AD found in eight databases between the beginning to July 2017.	To evaluate the effectiveness of acupuncture for the treatment of Alzheimer's disease.	Acupuncture was found to be effective, as it improved the score of clinical signs and symptoms of AD compared to the score before treatment in patients without	Current Medical Science

			other interventions.	
Shin et al., 2017.	Review of 19 studies, conducted between 2001 and 2016, on the effects of acupuncture and electroacupuncture on adult neurogenesis.	Examine studies on the effects of acupuncture and electroacupuncture on adult neurogenesis associated with the expression of neurotrophic factors in neurological diseases, in particular stroke, Alzheimer's disease and Parkinson's disease.	Although the association between adult neurogenesis and the improvement of neurological impairments remains ambiguous, increased expression of NTFs in the brain is seen after acupuncture. Considering this increase an extrinsic signal for neurogenesis, it could be promising as an additional treatment in various disorders.	Biochemical Pharmacology
Zheng et al., 2018	Clinical trial with 28 participants, 14 with AD and 14 healthy controls. From these groups, fMRI results were compared before, during, and after participants were stimulated with acupuncture.	Examining the effect of acupuncture on functional connectivity in AD using resting-state functional magnetic resonance imaging (rs-fMRI).	Acupuncture can induce significant regional changes in AD patients, such as modulation of spontaneous brain activity and enhancement of hippocampal connectivity.	PLoS One
Yan et al., 2019	Study protocol for a randomized controlled clinical trial. 60 patients with SCD were randomly separated into two groups, one receiving acupuncture and the other placebo needles.	Avaliar os efeitos da acupuntura na função cognitiva de adultos mais velhos com SCD, explorar o mecanismo central do efeito de longa-duração da acupuntura na SCD e investigara	Estudo ainda está em andamento, mas mostra que a acupuntura induz a proliferação celular no hipocampo.	BMJ Open

	for 12 weeks.	safety of acupuncture in SCD.		
Wa Cai, Wei-Dong Shen, 2018	Literature review of studies on the effects of acupuncture on anti-apoptosis in the treatment of neurological diseases. Articles published in PubMed between 2012 and 2017 were searched, so so that 117 articles were selected.	Understanding the antiapoptotic mechanisms of acupuncture for neurological diseases, including cerebral ischemia-reperfusion injury, AD, spinal cord and peripheral nerve injury, depression or stress, PD and intracerebral hemorrhage.	The antiapoptotic effect of acupuncture for neurological diseases is due to the distinct alteration of expression of Bcl-2, Bax, or caspase, reducing mitochondrial dysfunction, oxidative stress, and inflammation.	The American Journal of Chinesemedicine
Lai et al., 2020	Bayesa's pairwise and network meta-analysis. 7 banks were used to search for randomized clinical trials through September 2019. 9 comparative interventions were included. 28 trials were eligible, including 6,863 participants.	Compare and classify treatment methods for MCI and AD, in order to find an optimal intervention for MCI and a way to prevent or delay the occurrence of AD.	Among the nine treatments studied, music therapy seems to be the best treatment for ICM, followed by acupuncture.	Frontiers in Aging Neuroscience

Source: Alzheimer's Disease Cooperative Study - Activities of Daily Living: ADCS-ADL; Subjective cognitive decline: SCD; Alzheimer's disease: AD; Parkinson's disease: PD; Neurotrophic factors: NFTs; Neuropsychiatric Inventory: NPI; Resting-state functional magnetic resonance imaging: rs-fMRI; Mild cognitive disorder: MCI;

3 Results and Discussion

In order to better understand the evidence found on the role of acupuncture in the management of Alzheimer's disease, the articles were grouped by the authors based on the similarity between the main aspects addressed and are represented by the sub-items: efficacy and safety, modulation of neurogenesis, and comparison with other non-pharmacological interventions. As for the outcomes, most of the selected studies used



neuropsychological tests as a form of assessment, which include the scales universally used for the assessment of patients with AD, namely MMSE (Mini Mental State Examination), ADAS-cog (The Alzheimer's Disease Assessment Scale-Cognitive Subscale), CIBIC-plus (Clinician Interview-Based Impression of Change (Plus), ADAS-ADL (The Alzheimer's Disease Assessment Scale) and NPI (The Neuropsychiatric Inventory). In addition to these scales, we highlight the use of neuroimaging in studies that address the modulation of neurogenesis and functional connectivity, mainly through magnetic resonance imaging and functional magnetic resonance imaging, to evaluate the different domains that can be influenced by the acupuncture technique in the management of AD.

3.1 EFFICACY AND SAFETY

When it comes to the evaluation of a therapy for the management of some pathology, safety and efficacy are always questions of fundamental importance to be established. Currently, none of the drugs available for the treatment of AD can stop the progression of the disease, and their therapeutic effects are limited to the duration of treatment and subject to adverse events. Therefore, the available treatments have low efficacy and limited safety margin. Thus, since acupuncture has good results in neural protection and relatively few adverse effects, studies were reviewed with the intention of determining the feasibility of using acupuncture as a new therapy in the management of AD. In this context, a Chinese clinical trial conducted by Jia et al., (2017) compared acupuncture with donepezyl hydrochloride, which is one of the main pharmacological choices for AD. A total of 87 Chinese individuals aged 50 to 87 years were randomized into the control group, who received donepezilla alone, and intervention group, who received acupuncture therapy alone. Such a study indicated that acupuncture can improve cognitive function and overall clinical status according to ADAS-cog and CIBIC-plus scores, but its effect to improve activities of daily living and behavioral symptoms seemed to be limited based on ADAS-ADL and NPI scores (JIA, 2017). Thus, acupuncture was determined to be safe, well-tolerated, and effective for improving cognitive function and overall clinical





status in AD. However, these results, according to the authors, cannot provide evidence to prove that acupuncture therapy is better in efficacy than donepezil due to the small sample size.

According to a systematic review with meta-analysis by Wang et al. (2020), which included 3,099 articles, acupuncture associated with drug therapy may be more beneficial for AD patients than drug therapy alone, when areas of general cognitive function in the short and medium term were assessed. However, this study also had caveats, such as the fact that acupuncture alone did not have superior effects compared to drug therapy. Thus, the main points to note are that the efficacy of acupuncture was not shown to be superior to that of donepezil, but when associated, patients had better results on assessment scales, such as higher MMSE scores. However, another review with meta-analysis conducted by Huang et al. (2017), suggested significant superiority of acupuncture over drug therapy (donepezil) regarding the rate of efficacy according to scores on the MMSE, ADL and ADAS-cog scores. However, the authors themselves point out that all results should be interpreted with caution because none of the studies included in the meta-analysis were methodologically rigorous.

It is perceived that studies relating a placebo method of acupuncture (from English: "sham acupuncture") to effective acupuncture therapy are lacking. In this regard, a Chinese clinical trial by Yan et al. (2019), which is still in the participant recruitment phase, seeks to make this comparison. This study primarily targets patients with subjective cognitive decline (SCD), a preclinical stage of AD, for which there is no recommended pharmacological treatment (YAN, 2019). With the aims of evaluating the effects of acupuncture on cognitive function, exploring the central mechanism of the long-term effect, and investigating the safety of the method in these patients, 60 participants will be randomized into two groups. One group will receive acupuncture therapy and the other will receive placebo needles for 12 weeks, totaling 24 sessions. To evaluate the results, participants will undergo MRI and cognition tests before and immediately after treatment with acupuncture or placebo acupuncture..



3.2 Modulação da neurogênese e conectividade funcional

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Some of the principles guiding the applicability of acupuncture as a therapy for AD, justifying studies on its efficacy, are its effects on adult neurogenesis and brain functional connectivity. The review by Shin et al. (2019), proposes that the therapeutic efficacy of acupuncture is based on the stimulation of sensory nerve fibers, by the acupuncture point. A potent form of somatosensory stimulation and subsequent activation of physiological processes in the nervous system, such as release of neurotrophic factors that promote angiogenesis, facilitating neurogenesis and synapse formation. The neurotrophic factors increased by acupuncture are mainly BDNF (Brain Derived Neurotrophic Factor) and GDNF (Glia Derived Neurotrophic Factor). BDNF is a neurotrophin with a critical role in neuron survival and synaptic plasticity, modulating proliferation and differentiation of these cells. GDNF is a survival factor for dopaminergic neurons and also for the maintenance of central and peripheral neurons. On the effects of acupuncture on AD specifically, the study by Yan et al. (2019) determines that acupuncture induces cell proliferation along the dorsum of the alveus of the hippocampus and this is associated with improvement of cognitive deficits in mice with accelerated senescence, which show neuropathological features similar to AD. Thus, this research suggests that acupuncture can be used in synergy with pharmacological treatment to stimulate neurogenesis (YAN ,2019).

Resting-state functional magnetic resonance imaging (rs-fMRI) is a promising non-invasive imaging technique applied in the study of many neuropsychiatric disorders. This technique was used in a clinical trial by Zheng et al. (2018) that postulated that acupuncture can modulate or increase resting-state functional activity and connectivity of cognition-related regions, showing it to be an effective treatment for AD. In this study, increased connectivity between the right hippocampus and the left precentral gyrus was observed in AD patients when comparing post-acupuncture and pre-acupuncture stages. The hippocampus is one of the earliest pathological sites in AD and plays a crucial role in memory processes. These results provide evidence that acupuncture can induce significant regional changes in AD patients, including increased and decreased



spontaneous brain activity as well as enhanced hippocampal connectivity. These findings may be useful for further understanding the mechanisms of acupuncture and may provide a new method for the treatment of AD in the future (ZHENG, 2018).

According to Cai et al., (2018), progressive neuronal loss is one of the main characteristics of AD, thus, a specific treatment with the ability to inhibit excessive apoptosis may contribute to promote recovery from neurological diseases such as AD. In this sense, a review article of 117 publications sought to define the role of acupuncture in promoting antiapoptotic mechanisms as a management therapy for AD. The study demonstrated that the antiapoptotic effect induced by acupuncture is mainly reflected by increasing Bcl-2 expression and declining Bax and caspase expression. Significantly, Bcl-2 is the inhibitory factor of apoptosis, while Bax and caspase are apoptosis-promoting factors. Thus, the positive regulation of the Bcl-2 / Bax ratio has been considered a sign of an antiapoptotic mechanism, and therefore, acupuncture can be used along with other therapies to help and reduce the dose of drug administration, creating synergistic treatment effects for neurological diseases (CAI; SHEN, 2018).

3.3 Comparison with other non-pharmacological interventions

Non-pharmacological interventions in AD are still poorly studied but widely employed in the management of the disease. However, according to Lai et al., (2020), it remains unknown which of these interventions work, and to what extent they should be employed. The article points out that between 2013 and 2019, meta-analyses were conducted to evaluate the efficacy of cholinesterase inhibitors (the traditional pharmacological treatment employed in AD), including donepezil, galantamine, and rivastigmine, which suggested that this class has low efficacy in treating the early stage of Alzheimer's, that of Mild Cognitive Impairment (MCI). In addition, safety issues have been pointed out, so before recommending cholinesterase inhibitors for MCI, other methods should be considered. The Bayesian meta-analysis performed in this review, sought to thoroughly compare and rank the different treatments for MCI that help improve cognitive





function, for this, English and Chinese databases were analyzed. Some non-pharmacological therapies were included, such as acupuncture, music therapy, exercise therapy, lifestyle therapy, and nutritional therapy that had their effectiveness assessed using two MMSE and Adas-Cog scales. As a result, music therapy and acupuncture proved to be the most effective in the treatment of ICM, even when compared to pharmacological strategies, since the use of medications may present safety-related problems. However, the article highlights that more research is needed to evaluate not only the effectiveness of these interventions, but also to evaluate other interventions that were not included in this meta-analysis, such as mindfulness (LAI, 2020).

4 Final considerations

AD is a growing health problem, so it is essential that health professionals are prepared to properly manage these patients. However, the disease-modifying treatments, i.e., those that have been proven to change the pathology or its course, are not yet fully known (LANE; HARDY; SCHOTT, 2018).

In this scenario, the importance of investigating different therapies, such as acupuncture, is highlighted. This is reinforced by evidence suggesting that, unlike currently available pharmacological treatments, which have poor efficacy and limited safety margin, acupuncture has good results in neural protection and relatively few adverse effects. Furthermore, findings indicate that this form of therapy can improve cognitive function, general clinical status, influence spontaneous brain activity, enhance hippocampal connectivity, and stimulate adult neurogenesis.

However, the results found so far should be interpreted cautiously. This is because a significant number of the studies found were not methodologically rigorous, presenting, for example: small sample size and limitations regarding the comparison of the intervention with the placebo group.



Moreover, most of the studies found were conducted in China, making it difficult to generalize the results, since there is a limitation regarding the diversity of the population analyzed.

While these caveats are of paramount importance, it is noteworthy that acupuncture offers health professionals a promising and effective treatment option for AD. Thus, it is essential that further studies be conducted with greater methodological rigor, in order to establish an effective treatment for this disease, aiming to find ways to slow the progression of the disease and offer a higher quality of life for patients.

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