AGITATION RELIEF IN PATIENTS WITH ALZHEIMER’S DISEASE: A COMBINED APPROACH OF ACUPRESSURE AND CHOLINESTERASE INHIBITORS

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ABSTRACT

Introduction. Agitation is a common symptom in Alzheimer’s disease (AD). The traditional therapeutic technique of acupressure can be applied to improve the symptoms.

The objectives of this study were to evaluate the efficacy and safety of acupressure and donepezil for the treatment of agitation in patients with AD in comparison with donepezil plus risperidone.

Materials and methods. This randomized controlled trial was conducted in a hospital in Vietnam and enrolled willing participants who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for AD and presented with agitation symptoms between May 2020 and March 2022. Participants in each group were randomly assigned to receive acupressure plus donepezil or donepezil plus risperidone over 4 weeks.

Results. Of the 76 patients with AD presenting agitation symptoms who were randomized, 63 were included in the full analysis. After 4 weeks, the combined use of acupressure and anticholinesterase drugs significantly reduced agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI) scale.

RÉSUMÉ

Introduction. L’agitation est un symptôme courant de la maladie d’Alzheimer. La technique thérapeutique traditionnelle de l’acupression peut être appliquée pour améliorer les symptômes.

Les objectifs de cette étude étaient d’évaluer l’efficacité et l’innocuité de l’acupression et du donepezil pour le traitement de l’agitation chez les patients atteints de la maladie d’Alzheimer par rapport au donepezil plus rispéridone.

by 20.4% (p < 0.001). Similarly, it markedly alleviated the burden of caregiving, as measured by the Zarit Burden Interview (ZBI) scale, with a 14.7% reduction (p < 0.05). The intervention group did not significantly differ from the control group. No participant experienced severe adverse effects.

**Conclusions.** Our study showed that combining acupressure and the cholinesterase inhibitor donepezil effectively improved agitation symptoms and reduced caregiver burden in AD patients over a 4-week treatment period.

**Keywords:** Alzheimer’s disease, acupressure, agitation.

**List of abbreviations:**
- AD – Alzheimer’s disease
- DSM – Diagnostic and Statistical Manual of Mental Disorders
- ChEI – cholinesterase inhibitor
- AChE – acetylcholinesterase
- MMSE – Mini-Mental Status Examination
- CMAI – Cohen-Mansfield Agitation Inventory
- ZBI – Zarit Burden Interview
- TM – traditional medicine

**Introduction**

Alzheimer’s disease (AD) is the most common neurodegenerative disorder and accounts for 60-80% of all cases of cognitive decline; it causes severe disability and is a major cause of mortality among elderly people1–3. Its primary manifestations include a cluster of cognitive impairments that first affect memory functions, followed by psychological and behavioral symptoms that gradually interfere with daily activities4. Agitation is a behavioral symptom commonly associated with AD and occurs in 20.5% to 63% of cases5. It involves excessive verbal outbursts, tone, and actions that are sudden, inexplicable, and performed without a psychotic state6. There are presently no authorized guidelines or treatments for AD, despite the disease’s high risk of agitation7. Cholinesterase inhibitors (ChEIs) are the primary medications used to address cognitive symptoms and memory impairment in individuals with AD. By inhibiting acetylcholinesterase (AChE), these medications elevate acetylcholine levels, leading to increased neurotransmission activity in postsynaptic nerve terminals8. Among ChEIs, donepezil is a commonly used medication in Vietnam and was approved by Food and Drug Administration in 1996 for treating mild to moderate AD. For AD patients exhibiting agitation symptoms, the antipsychotic drug risperidone has been evaluated for its effectiveness and low side effects in managing agitation in these individuals9,10.

Traditional medicine has been commonly applied to promote health in Vietnam11. In addition to medication-based treatments, acupressure is a distinctive nonpharmacological therapeutic approach in traditional medicine (TM). It involves stimulating specific acupoints in the body to treat diseases and enhance blood circulation within the body’s meridians, regulating the functions of related organs, and aiming to prevent and treat diseases12,13. Prior reviews suggest that acupuncture may reduce agitation in AD patients14,15. Preliminary randomized clinical trials demonstrated that acupressure at specific acupoints, such as Fengchi, Baihui, Shenmen, Neiguan, and San Yin Jiao, improved agitation symptoms, as measured by the Cohen-Mansfield Agitation Inventory (CMAI) scale16. Another study indicated that acupressure at acupoints Fengchi, Yintang, Shenmen, Neiguan, and Baihui in AD patients with agitation improved agitation symptoms and reduced stress by decreasing salivary cortisol levels17. To the best of our knowledge, no studies have been conducted on the effects of acupressure in conjunction with ChEI or antipsychotics (risperidone and donepezil) in patients with AD who exhibit agitation symptoms.

**The objective of the study** was to evaluate the safety and effectiveness of a particular therapeutic approach in reducing agitation in AD patients.
approach involving the combination of acupressure and ChEI for patients suffering from AD. Additionally, this study aimed to determine whether this treatment combination can reduce the burden on caregivers.

**Material and methods**

**Study design**

This randomized controlled trial was conducted from May 2020 to March 2022 at 30-4 Hospital, Ho Chi Minh City, Vietnam. The trial was performed for 4 weeks, and the study was approved by the Ethics Council for Medical Research at the University of Medicine and Pharmacy at Ho Chi Minh City (No. 543/HDDD-DHYD).

**Participants**

Participants were recruited from the Memory and Cognitive Impairment Unit. Participants were considered eligible if they were diagnosed with AD and presented with agitation symptoms (such as restlessness, wandering, or aggression occurring at least twice a week for a minimum of two weeks\(^\text{18}\) based on Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria\(^\text{19}\) and met the criteria of the Mini-Mental State Examination (MMSE) score ranging from 10 to 26 points\(^\text{20}\). Additionally, participants had to have a caregiver who was a family member (such as a spouse, child, or grandchild) and who was directly involved in the patient’s care, including taking them to medical appointments, helping them take their medication, and providing emotional and mental support. All participants joined the trial voluntarily. Patients with acute diseases such as infections or electrolyte disorders, those who were newly diagnosed with mental illness, or those who refused to participate were excluded from the study.

The random distribution method was employed to generate a blocked randomization list of study participants with a random seed, utilizing blocks of sizes 2, 4, and 6. Seventy-six eligible patients who met the selection criteria and agreed to participate in the research were randomly allocated into two groups: the intervention group (acupressure + donepezil) and the control group (donepezil + risperidone) (n = 38 each). Due to the impact of the COVID-19 pandemic, six patients from the intervention group and seven patients from the control group discontinued their participation in the study. The research results were analyzed based on data obtained from 32 patients in the intervention group and 31 patients in the control group. None of the patients discontinued the study due to adverse events related to the intervention or the emergence of unfavorable concurrent medical conditions that necessitated alternative treatment pathways. The process of harvesting the research data is presented in Figure 1.

**Intervention process**

The patients in this group received 5 mg of donepezil (1 tablet per day) after their evening meal,
which was administered by their caregivers. Patients also received acupressure treatment from a trained therapist once a day, five days a week, for four consecutive weeks. The therapist applied pressure to five acupoints, namely, Shenmen, Neiguan, Baihui, Yintang, and Fengchi. The acupressure duration was 15 minutes per session, with patients positioned either supine or seated. The fleshy part of the thumb stimulated the Shenmen point, while the Baihui point on the same side was also stimulated simultaneously through slow and gradual movements from superficial to deep pressure. This process continued until the patient felt a sensation of qi, which is usually manifested by furrowed brows or a contracting expression, and the therapist maintained pressure on the points. Gentle stimulation was applied to avoid discomfort. The total duration for each point was 5 minutes, with 5 minutes for the Shenmen point initially, followed by concurrent stimulation of the Baihui and Fengchi points for 5 minutes, concluding with simultaneous stimulation of the Neiguan and Yintang points for 5 minutes. For bilaterally symmetrical points (Fengchi, Neiguan, Yintang), one side was stimulated during a session, while the other side was stimulated in the subsequent session.

**Control Group:** Patients in the control group received two types of medication, 5 mg of donepezil (1 tablet per day) and 1 mg of risperidone (1 tablet per day), after their evening meal at home, administered by their caregivers.

**Monitoring and Assessment**

The data of both groups were collected every two weeks throughout the four-week treatment period.

The **Mini Mental Status Examination (MMSE)** was used to screen for Alzheimer’s disease and other cognitive impairments, with a minimum score of 0 and a maximum of 30. The lower the score is, the more severe the patient’s disease. The ordinal variable has 4 values corresponding to the stage of AD.

**Cognitive subscale in the MMSE:** The MMSE scale has many subscales corresponding to cognitive functions, including force orientation (time + place; score from 0–10), memory (0–6), language (0–8), attention focus (0–5), and spatial vision (0–1). The score is equal to the sum of the subscales combined, with the largest being 30 and the lowest being 0.

The **Cohen-Mansfield Agitation Inventory (CMAI)** consists of 29 items measuring the severity of symptoms of psychobehavioral disorders; the score ranges from 1 to 7, and the minimum score ranges from 29 to a maximum of 203. The higher the score was, the more severe the level of agitation was in people with AD.

The **Zarit Burden Interview (ZBI)** was used to measure caregiver burden and consisted of 22 self-assessment questions, each consisting of 5 options on a Likert scale ranging from 0 to 4 points. The total score ranged from 0 to 88. The higher the score is, the greater the burden of care.

Additionally, the occurrence of adverse events such as nausea/vomiting, diarrhea, bradycardia, fatigue, hand tremor, pain, and drowsiness was recorded based on reports from patients or caregivers.

**Data analysis**

The data were entered and managed using Microsoft Excel, while the statistical analysis was performed using R.4.1.1 software. To compare the mean values of two independent groups, we used the independent sample t test or Wilcoxon test (for nonnormally distributed data). To assess changes in the mean values before and after treatment, we employed paired t tests. When the assumptions of the t test were not met, the Wilcoxon test was used. Additionally, we assessed differences between proportions using the chi-square test. If the expected frequency was less than 5 and accounted for more than 20% of the 2xn table, we used Fisher’s exact test as an alternative.

To evaluate differences between the two treatment methods in the repeated-measures design, we used a mixed effects model. When assumptions regarding variance homogeneity and covariance were not met, we used the Greenhouse-Geisser correction method to adjust for the impact of the interaction between time and treatment group for the independent variable at three different time points.

**Results**

**Characteristics of participants**

According to the information presented in Table 1, the median ages of the participants in the intervention and control groups were 68 and 66 years, respectively. However, this difference was not statistically significant (p > 0.05). A greater proportion of participants were female than male. There was no significant difference in the sex distribution between the two groups (p > 0.05). The marital status of the participants was female than male. There was no significant difference in the marital status between the two groups (p > 0.05). The average duration of illness in both groups was 3.2 years, ranging from 1 to 9 years.

There was no significant difference in the distribution of disease duration between the two groups (p > 0.05). The study showed that late-onset cases were more prevalent, with a ratio of 1:1.7, than early-onset cases were. There was no significant difference in the distribution of onset types between the two groups (p > 0.05). The marital status of the participants did not significantly differ between the two groups (p > 0.05), with most participants being married.
married in both groups. The study also revealed that a family history of AD was more prevalent among those with a history of this disease than among those without, without a significant difference in the distribution of family history between the two groups (p > 0.05). Comorbidities such as hypertension, diabetes mellitus, and dyslipidemia were most prevalent, but their distributions did not significantly differ between the groups (p > 0.05).

### Characteristics of the MMSE scores of AD patients

Among the 63 AD patients in our study, the average MMSE score ranged from a minimum of 10 to a maximum of 26 (Table 2). The difference between the two groups was not statistically significant (p > 0.05). The various cognitive domains, including orientation, memory, attention, language, and spatial visual perception, of the 63 AD patients in both groups, as measured by the MMSE scale, were affected. Nevertheless, the difference between the two groups was not statistically significant (p > 0.05).

### Alterations in agitation levels according to the CMAI scale

In the intervention group, the average CMAI score significantly decreased after both 2 and 4 weeks of treatment compared to the initial score (p < 0.01). At 2+6 weeks, the average score was 6.38 ± 2.78 points (a 13.8% decrease from the start), and at 4+6 weeks, it was 4.14 ± 4.34 points (a 20.4% decrease from the start). Similarly, in the control group, the average CMAI score significantly decreased after 2 and 4 weeks of treatment compared to the initial score (p < 0.01). At 2+6 weeks, the average score was 5.87 ± 3.79 points (11.9% decrease from the start), and at 4+6 weeks, it was 4.87 ± 4.43 points (19.7% decrease from the start). Figure 2 depicts the variations in agitation scores measured by the CMAI scale across three periods: before treatment, after 2 weeks, and after 4 weeks. Initially, there was no noteworthy difference in the CMAI score between the groups. After 2 weeks, the score of the intervention group decreased by 13.8% from the baseline, while that of the control group decreased by 11.9%. After 4 weeks, the intervention group showed a 13.8% reduction, while the control group had a 19.7% decrease. Thus, at both the 2-week and 4-week assessments, the intervention group displayed a greater decrease in agitation scores than did the control group.

When analyzing the difference in changes in CMAI scores between the two methods using a mixed-effect model, we observed a deviation from the sphericity assumption (Mauchly’s test of sphericity, χ² = 0.015) with an Epsilon Greenhouse-Geisser value of 0.89. Following Greenhouse-Geisser correction,
Figure 1. Study flow chart

Figure 2. Alterations in agitation levels according to the CMAI scale (Note: A paired t test)
the adjusted p-value was 0.57. Therefore, based on data from 63 patients collected across three time points, we cannot confidently claim statistically significant differences in the effectiveness of the intervention compared with conventional methods concerning changes in agitation levels measured by the CMAI scale.

The alteration of caregiver burden according to the ZBI

In the intervention group, ZBI scores significantly decreased after 2 weeks and 4 weeks of treatment (p < 0.01). After 2 weeks, the scores decreased by 7.1% (2.94±4.68 points), and after 4 weeks, they decreased by 14.7% (5.66±6.94 points). In the control group, the scores also decreased significantly after 2 and 4 weeks (p < 0.05). After 2 weeks, the decrease was 3.7% (1.32±3.02 points), and after 4 weeks, it was 13.4% (9.87±4.43 points). Figure 3 displays changes in caregiving burden scores measured by the ZBI across three time points: before the study, after 2 weeks, and after 4 weeks of treatment. Initially, there was no significant difference in ZBI scores between the groups. After 2 weeks, the percentage in the intervention group decreased by 7.1%, while that in the control group decreased by 3.7%. After 4 weeks, the intervention group showed a 14.7% reduction, and the control group decreased by 13.4%. Thus, at both the 2-week and 4-week evaluations, the intervention group exhibited greater reductions in caregiving burden scores measured by the ZBI scale than did the control group.

When comparing the change in ZBI scores between the two methods using a mixed-effects model, we observed a lack of sphericity in the model (Mauchly’s test of sphericity, p = 0.00), with an Epsilon Greenhouse–Geisser value of 0.66. After applying the Greenhouse–Geisser correction, the adjusted p-value was 0.22. Consequently, based on data collected from 63 patients across three data collection time points, there is not enough evidence to support statistically significant differences in the effectiveness of the intervention versus conventional methods in altering caregiving burden levels measured by the ZBI scale.

Adverse events

A few adverse events are presented in Table 3. In the intervention group, 6.3% of the patients experienced nausea/vomiting, 3.1% had diarrhea, 3.1% felt drowsy, 9.4% experienced fatigue, and 6.3% felt pain. No mild bradycardia was observed during treatment. Similarly, the control group had a low incidence rate: 3.2% had nausea/vomiting, 3.2% diarrhea, 6.5% fatigue, 6.5% drowsiness, and 2% hand tremors. Our findings align with the results of Dunn et al. on donepezil’s side effects in AD patients, noting nausea (1.61%), vomiting (1.5%), and fatigue (0.74%)24. Moreover, the intervention group also did not experience changes in heart rate, and all symptoms were mild; moreover, the intervention process was not affected, and the patients did not warrant discontinuation of the study. A previous trial of 529 AD patients revealed adverse events related to donepezil in 32 participants: diarrhea (1.32%), nausea (0.95%), and sleep disturbances (0.95%)25. ChEIs effectively treat AD but may cause transient nausea, vomiting, and diarrhea because of increased cholinergic nerve transmission26. In our study, tremors resulting from risperidone use were rare. Risperidone reduced behavioral disturbances in AD patients, aligning with Negrón AE’s findings27.

DISCUSSION

In the intervention group, agitation, measured on the CMAI scale, decreased by 13.8% after 2 weeks and 20.4% after 4 weeks, significantly improving with acupressure and ChEIs (p < 0.01). The control group, who received ChEIs and antipsychotic medication, showed a reduction of 11.9% at 2 weeks and 19.7% at 4 weeks. Comparing both groups, the reductions in agitation were 13.8% vs. 11.7% at 2 weeks and 20.4% vs. 19.7% at 4 weeks, but these differences lacked
statistical significance, potentially due to the small sample size and the short duration of the study. Our findings align with Kwan Rick’s research on the efficacy of acupressure for dementia-related agitation, which was observed from week 4 to week 67.

The use of acupoints such as Fengchi, Yintang, Shenmen, Neiguan, and Baihui is associated with manifestations of various organ illnesses and effectively improved agitation symptoms in our study. According to traditional medicine theory, acupressure at Baihui University positively influences mental clarity and memory retention and may reduce agitation behaviors. Fengchi, Yintang, Shenmen, and Neiguan play roles in enhancing circulation, calming the spirit, boosting energy, and aiding neurological recovery, respectively13,28,29. Risperidone showed efficacy in treating agitation but demonstrated adverse effects at higher doses, notably extrapyramidal symptoms in some patients27.

In the intervention group, ZBI scores were reduced by 7.1% at 2 weeks and 14.1% at 4 weeks with acupressure and ChEI (p < 0.05), easing caregiver burden. The control group, who received ChEI and antipsychotic medication, showed a reduction of 11.9% at 2 weeks and 13.4% at 4 weeks on the ZBI scale. Comparing both groups, the reductions were 7.1% vs. 11.7% at 2 weeks and 14.1% vs. 13.4% at 4 weeks, but these differences lacked statistical significance, likely due to study limitations—a small sample size and a short duration. Caregivers have numerous duties, including medical care, chores, and managing finances30. These responsibilities significantly impact their health and quality of life31.

There are several limitations in our study; we were not able to monitor the recurrence rate after 4 weeks of treatment. Additionally, this study was conducted solely in the hospital setting and not in a clinical setting or nursing home, where many Alzheimer’s disease patients may experience agitation, which can harm both patients and caregivers. Therefore, we recommend that future studies aim to overcome these limitations, including conducting multicenter studies in nursing homes, increasing the sample size, lengthening the study duration, and monitoring recurrence after treatment.

**Conclusions**

The study concluded that acupressure, when used in combination with ChEI, can be an effective alternative for managing agitation symptoms and reducing caregiver burden in AD patients. The improvements observed in the patients were like those achieved through conventional medicine. Furthermore, both the intervention group and the control group demonstrated a favorable safety profile with minimal adverse events. However, additional studies and larger-scale studies are necessary to validate and extend these findings.

**Author Contributions:**


**Compliance with Ethics Requirements:**

“The authors declare no conflict of interest regarding this article”

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study”

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**Reference**


