Review

Acupressure and Dementia - A Review of Current Evidence

Soo Liang Ooi, Gillian Drew, Sok Cheon Pak *

School of Dentistry & Medical Sciences, Charles Sturt University, Panorama Avenue, Bathurst, NSW 2795, Australia

***Correspondance:** spak@csu.edu.au; Tel: 61-2-6338-4952 Fax: 61-2-6338-4993

ABSTRACT

Introduction: Dementia is a cognitive decline with patients often exhibit behavioural and psychological symptoms, severely affecting the quality of life and placing a heavy burden on caregivers. Acupressure has reported benefits for dementia. This study aims to critically review the available evidence for its use as a non-pharmacological therapy.

Methods: Systematic search of major research databases for human clinical trials using acupressure as an intervention for dementia patients was conducted. Results were synthesised for the effects of acupressure on various outcome measures of interest for dementia.

Results: Twelve clinical trials (N=973), including eight randomised control studies, were included in this review. The study sample was predominantly institutionalised residents with moderate to severe dementia. Baihui (GV20), Shenmen (HT7), Fengchi (GB20), Neiguan (PC6), Sanyinjiao (SP6), and Yingtang (EX-HN3) were the most used acupoints for intervention. Acupressure techniques employed in these clinical trials vary greatly with no standardised approach.

This review finds inconsistent evidence in the effectiveness of acupressure in reducing agitation and behavioural disturbances. However, the treatment appears to improve their ease of care and reduce physical stress. Affixing acupressure devices on selected acupoints can also potentially improve psychiatric pain, anxiety, and depression. Long-term (6 months) treatment can potentially improve the cognitive function, activities of daily living, and quality of life of patients with mild to moderate dementia. The effect of acupressure on sleep disturbances remains unclear.

Conclusion: More high-quality research on acupressure is needed to fill the gaps in knowledge and inform better care for dementia patients in the future.

Keywords: Acutherapy, geriatric therapy, Alzheimer's disease, sensory stimulation, evidence-based practice.

1 Introduction

Dementia is a collective term used to describe various symptoms of cognitive decline due to diseases or degenerative brain disorders. The prevalence of dementia is between 5%-7% of the world population aged 60 and above [1]. In 2016, 43.8 million individuals were living with dementia globally. This number is increasing due to the ageing population and will reach 65.7 million in 2030 and 115.4 million in 2050 [1,2]. In Australia, dementia affects approximately one in ten older people aged over 65 and half of the permanent aged care residents [3]. With the decline of cognitive function, many aspects of the life of dementia patients are negatively affected, resulting in the eventual loss of ability to perform activities of daily living (ADL) [4].

Patients with dementia often exhibit agitation, depression, apathy, repetitive questioning, psychosis, aggression, sleep problems, wandering, and a variety of socially inappropriate behaviours. These are signs and symptoms of disturbed perception, thought, mood, or behaviour, referred to as behavioural and psychological symptoms associated with dementia (BPSD) [5,6]. The cause of BPSD is unknown. The known contributing factors that increase vulnerability are prior psychiatric illnesses, stress derived from physical, mental, or emotional origins such as pain and sleep problems, lack of exercise or routine, and deficiencies in care received [5,7].

As no treatment can reverse the neurodegeneration, individuals who have dementia, their family, and society faced a heavy burden [2,8]. Antipsychotic drugs remain the primary strategy to manage BPSD in clinical practice, even though non-pharmacological interventions are the recommended approach [5,7,9,10]. Pharmacologic management is preferred due to the lack of experience with or perceived lack of efficacy of non-pharmacological interventions by the clinicians [7], albeit the use of psychotropic medications comes with increased risk of falls and impaired cognitive function [11].

Acupressure is a therapy where pressure is applied to one or more acupoints along the meridians of the body to balance the flow of physiological energy or *qi* [12]. Like acupuncture but without the use of any needle, acupressure is originated from ancient China and widely used in Traditional Chinese Medicine (TCM). Stimulation of acupoints with pressure can lead to complex neurohormonal responses including the reduction of cortisol production, increasing serotonin transmittance to the brain, and the release of β-endorphins from the hypothalamus and pituitary into the spinal fluid and the bloodstream [12,13]. These physiological responses induce relaxation and produce analgesic and sedative effects [12–14]; hence, acupressure is a non-intrusive therapy for treating a wide range of conditions and promoting individual wellbeing, especially for older adults [12]. Among non-pharmacological interventions for BPSD, acupressure is considered a form of sensory stimulation therapy [15,16] similar to manual massage [17,18] that can potentially increase alertness, reduce agitation, and enhance the quality of life (QoL) of dementia patients. This review critically analyses the current evidence on the use of acupressure as an intervention for people with dementia, based on results from available clinical trials.

2 Methods

A systematic literature search was performed between March and June 2020 using major research databases (Pubmed, EBSCOhost, PsycInfo, ProQuest, Scopus, Web of Science, Cochrane Library, and CINAHL Plus) with the search terms ‘acupressure’, ‘acupoints AND pressure’, ‘acupuncture points AND pressure’ together with ‘dementia’, ‘Alzheimer’, ‘senile’, ’mental deterioration’. References of the full-text articles assessed for eligibility were also searched manually to locate additional articles not indexed by the databases. A sample query with MeSH terms and keywords using Pubmed can be found in Supplementary 1.

The criteria of inclusion were (1) clinical trial, (2) participants were dementia patients, (3) acupressure as a therapeutic intervention either

 doi:10.20944/preprints202108.0532.v1

as a monotherapy or in combination with other interventions, (4) outcome measures are one or more aspects of BPSD, ADL, cognitive function, biomarkers, or QoL. The search included any therapeutic forms that involve applying pressure with fingers or devices to one or more acupoints throughout the body. The practice of Shiatsu, even though incorporating touch and pressure of acupoints, was explicitly excluded due to the dissimilarities in philosophy and technique, as noted by Cabo et al. [19]. Included clinical trials were synthesised for the effects of acupressure on different outcome measures of interest in patients with dementia, including agitation, behavioural disturbances, cognitive functioning, ability to perform daily living activities, sleep, pain, anxiety, mood, quality of life, ease of care from the carers' perspective, and any relevant biological markers.

3 Results

3.1 Search results

Figure 1 is a summary of the literature search flow. The search found 92 unique records after removing duplicates. After screening the abstracts, 35 full-text articles were assessed for eligibility resulting in 15 reviews or commentaries as well as two articles on Shiatsu excluded. Sixteen articles discussing the designs or findings of 12 clinical trials were analysed qualitatively. Among the studies, eight are randomised controlled trials (RCTs) [20–27] as summarised in Table 1. The remaining four are quasi-experimental studies [28–31] with characteristics listed in Table 2.

3.2 Study population

The 12 clinical trials included a total of 973 participants with the pooled mean age being 81.10±6.74 with 48.2% male and 51.8% female. All the trials recruited participants from institutionalised dementia residents except one [21], which recruited dementia patients in community care. Four studies [21,22,28,30] specifically recruited participants diagnosed with Alzheimer's disease (AD). In contrast, the rest included patients with dementia due to any type of neurological conditions, mainly according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders Version 4) criteria. The localities of research were: Taiwan (3 trials, n=339), Hong Kong (3 trials, n=203), China (2 trials, n=158), Italy (1 trial, n=129), Spain (1 trial, n=111), Japan (1 trial, n=23), and United States (1 trial, n=10). The participants included in these clinical trials were predominantly (71.9%) from the Greater China region.

3.3 Acupoints and techniques

A total of 19 acupoints, as listed in Table 3, were identified as the intervention points. The most used were Baihui (GV20), Shenmen (HT7), Fengchi (GB20), Neiguan (PC6), Sanyinjiao (SP6), and Yingtang (EX-HN3). Expert TCM practitioners also recommended these acupoints for the treatment of agitation in people with dementia as reported by Kwan et al. [32] during the design of acupressure protocol through Delphi method for their clinical trials [25,31].

Acupressure techniques utilised in these clinical trials vary greatly. The trials conducted in the Greater China region [20,21,24–27,29,31] generally conformed to the TCM technique, which involved applying pressure with hands or thumbs at a series of acupoints during a treatment session. There were, however, differences in terms of acupoints, durations and frequencies of sessions, as well as add-on techniques such as warm-up activities [20,24,27], essential oil [24,27], or ear, thumb, and toe massage [21]. The session durations range between 9 to 20 minutes, and treatment frequencies were either once [20,24,28,31] or twice [21,25,26,29] daily, with only one study utilising a bi-weekly intervention frequency [27]. Most studies only offered a brief overview of the treatment protocol except Fung and Tsang [27], which published a detail description. The RCT by Kwan et al. [25,33] was preceded with a rigorous development process involving expert consensus through Delphi method [32] and conducting a pilot study [31] to determine the appropriate treatment duration and frequency.

 doi:10.20944/preprints202108.0532.v1

Other acupressure techniques were (1) gentle touch of a single acupoint (Shenzhu GV12) with palm for three minutes [22]; (2) auricular acupressure with seeds at multiple ear acupoints [23]; (3) foot massage with acupressure at four acupoints (unspecified by the authors) [28]; and (4) administering a specialised device at a single acupoint (Shenmen HT7) for eight hours a day [30].

3.4 Effects by outcome measures

3.4.1 Agitation

Six studies [20,24,25,27,29,31] assessed the effects of acupressure on agitation manifested in dementia patients using the Cohen-Mansfield Agitation Inventory (CMAI). The CMAI is a 29-item scale that systematically assesses the physically aggressive, physically nonaggressive and verbally agitated behaviours due to cognitive impairment [34]. Patients with total CMAI scores of 15 and above are considered 'agitated' [35].

In a cross-over pilot study by Yang et al. [29], four weeks of acupressure treatment significantly reduced the overall agitated behaviours ($p<.001$) of 20 participants who had severe agitation at baseline (total CMAI score ≥ 40). The post-test CMAI scores, when compared between the control and experimental phases, were also significantly different ($p<.001$) across all domains. This study, however, suffered from several limitations, including small sample size, lack of randomisation, unblinded assessors, and a high dropout rate of 35.5%.

Lin et al. [20] compared acupressure to Montessori methods and physical presence in a cross-over RCT among 133 institutionalised dementia patients with severe agitation (CMAI total score ≥35). Four weeks of acupressure treatment or Montessori methods were found to significantly decrease overall agitated behaviours ($p=.001$), aggressive behaviours ($p=.001$) and physically nonaggressive behaviours ($p=.02$). In contrast, the mere physical presence of another person did not affect the agitated behaviours of the participants. This study overcame many of the limitations of the previous study by Yang et al. [29]; however, risks of bias remained with cluster-randomisation at the institution level only, and it was unclear how the researchers achieved double-blinding.

In a newer RCT conducted by the same group of researchers, Yang et al. [24] compared the combined treatment of acupressure and aromatherapy (aroma-acupressure) to aromatherapy with routine care as a control. A total of 186 participants with dementia and severe agitation (total CMAI score ≥35) were allocated to receive one of three treatments. Both the aroma-acupressure and aromatherapy groups experienced significant improvement ($p<.001$) in agitation after four weeks of treatment. The mean agitation scores remained significantly lower ($p<.001$) than the baseline scores in both intervention groups after three weeks [24]. No significant change in agitation was detected in the control group throughout the study. This study was criticised for having non-equivalent groups at baseline whereby the groups' sizes vary and differed in mean age and dementia diagnostic categories significantly ($p<.01$) [36]. The mean pre-test CMAI score of the aroma-acupressure group also had a difference more than a standard deviation compared to the mean of the control groups. Furthermore, randomisation was done at the institution level, but individuals were the unit of analysis. These limitations cast doubt on the cause and effect relationship between the study's positive findings and the interventions [36].

In a small study using time serial design with 24 agitated dementia patients divided into eight dosage-combination groups, Kwan et al. [31] found treatment with nine minutes of acupressure either once or twice a day significantly reduced agitation after the first week($p<.001$). The most substantial effects were observed when acupressure was done twice a day ($p=.026$) for two weeks ($p=.005$). The results of this pilot study informed the design of a larger RCT [25] which compared acupressure to sham and usual care with 119 dementia participants with agitation. Contrast to the earlier findings, acupressure treatment for two weeks did not demonstrate any significant effect in the reduction of agitated behaviours compared to sham or control. Similarly, in another RCT by Fung

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and Tsang [27] that combined acupressure with aroma-massage to compare with cognitive training and exercise as controls, no significant difference in CMAI scores was detected across all groups at baseline, after three weeks of treatment, and three months after treatment.

To summarise, acupressure appeared to reduce the agitation behaviours in patients with dementia with evidence supported by two observation studies [29,31] and two RCTs [20,24]; however, these studies suffered from methodological limitations. Whereas in another two RCTs [25,27], acupressure did not demonstrate any significant effect on agitation when compared to sham, cognitive training and exercise. As such, the effect of acupressure on the agitated behaviours among dementia patients remains inconclusive.

3.4.2 Behavioural disturbances

Sutherland et al. [28] assessed the effects of foot acupressure and massage on the behaviours of ten patients with AD. The study found that ten minutes of foot acupressure and massage once a day for ten days appeared to reduce wandering while increasing their quiet time after treatment. The differences, however, were not statistically significant due to the small sample size. This study utilised a custom-designed behavioural documentation instrument.

The behavioural disturbances of dementia patients are more commonly assessed with the Neuropsychiatric Inventory (NPI) which evaluates 12 domains: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, nighttime behaviour disturbances, as well as appetite and eating abnormalities [37]. Three studies evaluated the effects of acupressure on these behavioural disturbances in dementia patients using the NPI.

Simoncini et al. [30] utilised a specialised device with a small, smooth, and soft plastic button fixed to a patch to create and sustain a constant pressure on the Shenmen HT7 acupoint for an extended time in an observational study. Each of the 129 participants had a pair of the devices affixed to both wrists every evening at 30 minutes before sleep and removed the next morning after eight hours. The mean NPI score of the participants at the end of the treatment period after two months reduced significantly ($p<.001$) from baseline. The mean NPI score remained low at four months after treatment.

In the study by Mariko et al. [22], twenty-three moderate to severe dementia patients with BPSD were randomly assigned to acupoint touch treatment twice daily for four weeks or served as controls. The treatment involved gently touching the Shenzhu GV12 point at the back, located below the third thoracic vertebrae, for three minutes using the palm over clothes and ended with a gentle massage around the point. Neuropsychiatric disturbances assessed with mean NPI score were reported to reduce significantly in the intervention group ($p<.05$), but not in the control group, after four weeks of treatment, when compared to baseline.

In the study by Fung and Tsang [27], sixty dementia patients who had BPSD were randomly assigned to three treatment groups of equal sizes: (1) aroma-massage with acupressure and exercise, (2) cognitive training and exercise, (3) aroma-massage with acupressure and cognitive training. The neuropsychiatric disturbances of the participants were assessed with NPI at baseline, after a treatment period of three weeks (post-test), and three months after treatment (post-3-months). Statistically significant reductions in the mean NPI severity score were detected in Group 1 at post-test ($p<.01$) and at post-3-months ($p<.01$), compared to baseline. For Group 3, the mean NPI severity score reduction at post-3-months was significantly lower than baseline ($p<.05$). As for NPI distress score, both groups treated with aroma-massage plus acupressure had significantly lower means at post-3-months versus the means at baseline ($p<.01$). In comparison, no significant changes in both NPI severity and distress scores were observed in the control group (Group 2). Acupressure plus aroma-massage was found to have overall significant effects in reduction of the NPI severity score ($p=.04$, $f=2.889$, $df=2$, observed power=0.69) and distress score ($p=.04$, $f=3.022$, $df=2$, observed power=0.68). However, there were dissimilarities in the participants across groups. Group 1 consisted of participants with

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higher attention score (p<.04) and better ADL score (p<.01) at baseline. After adjusting for baseline attention and ADL scores, the results became not statistically significant.

Evidence from an observational study [30] and a small RCT [22] supports the use of acupressure for behavioural disturbances in dementia, but the benefit was not demonstrated in a larger RCT [27]. Likewise, the real effect of acupressure on behavioural disturbances of dementia remains unclear.

3.4.3 Cognitive function

Five studies assessed the effects of acupressure on the cognitive function as measured by the Mini-Mental State Examination (MMSE), a standard clinical tool for cognitive assessment through evaluation of the mental abilities [38]. In an RCT of 80 community dementia patients, Wan et al. [26] reported statistically significant (p<.05) improvement in the cognitive function of the acupressure group. The mean MMSE score increased from 19.51±2.86 at baseline to 21.67±2.24 after six months of treatment. A 1-3 points difference in MMSE score can be considered clinically significant [37]. No significant change was detected in the control group that received only routine care. The cognitive improvement of the acupressure group also reflected in a significant improvement (p<.05) in the mean severity score of dementia measured with the Hasegawa's Dementia Scale over baseline.

There was, however, no evidence suggesting that acupressure treatment had any effect on the cognitive function in studies by Mariko et al. [22], Rodriguez-Mansilla et al. [23], Fung and Tsang [27], and Simoncini et al. [30]. These studies did not detect any statistically significant difference in the mean MMSE scores of the participants at baseline and those at post-intervention time points. Nevertheless, Rodriguez-Mansilla et al. [23] noted a weak relationship between treatment and MMSE since patients with moderate dementia (MMSE score: 19–15) appeared to respond better to acupressure treatment than those with severe dementia (MMSE score: ≤14).

The study by Wan et al. [26] has two distinctive differences compared to other studies. Firstly, the study included only patients with mild to moderate dementia under community care, whereas the other studies included institutionalised patients with moderate to severe dementia. Secondly, the acupressure treatment duration lasted six months, whereas all other studies had treatment durations of three months or less. Hence, long-term acupressure treatment (6 months) may be a causative factor in reversing the cognitive deterioration of patients with mild to moderate dementia under community care. Such observation requires validation in further research.

3.4.4 Activities of daily living

The ability to perform ADL is a crucial determinant for the level of care required by dementia patients. Five studies [21,22,26,30] included assessment of ADL of the participants as outcome measures with two of them [21,22] used Barthel Index (BI) for ADL evaluation. BI is an ordinal scale that assesses ten variables describing ADL and mobility and a higher BI score reflects a better ability to function independently [39].

Wang and Kui [21] studied the ADL performance of 78 dementia patients admitted to a TCM hospital. The patients were randomly assigned to two equal-sized groups. The treatment group received acupressure intervention twice daily for six months in addition to routine care, whereas the control group received only routine care over the same period. The participants were grouped into three ADL categories based on their BI scores: (1) Good (>60), (2) Medium (41-60), and (3) Low (≤40). Both groups had no members in the Good ADL category at baseline, and there was no significant difference in distribution between groups. After six months of treatment, 23 patients in the acupressure group achieved Good ADL category, compared to only 16 in the control group. The between-group difference in distribution was significant (p<.05). The mean age of the patients was younger in this study (69.2±5.32 in the invention group and 68.9±4.26 in the control group) compared to other included studies in this review. The other study which

utilised BI for assessment of ADL was conducted by Mariko et al. [22] in an older dementia cohort (mean age 82±9). Conversely, this study did not find any significant change in mean BI score before and after acupressure treatment.

The potential benefits of acupressure on ADL were also demonstrated by Wan et al. [26]. The study utilised a modified ADL instrument for dementia to assess the ADL of community dementia patients in six categories of nutrition, hygiene, function, daily living, dressing, and safety. The study found improvement in the mean ADL score in the acupressure group relative to baseline after completed six months of treatment ($p<.05$). No significant change in ADL was detected in the control group.

Simoncini et al. [30] used Katz ADL that evaluated the functional status of dementia patients based on their abilities to perform bathing, dressing, toileting, transferring, continence, and feeding [40]. The study also used the Lawton Instrumental ADL (IADL) scale to assess the participants' ability to perform complex ADL, including using a telephone, doing laundry, and handling finances [41]. No significant differences between the means of Katz ADL and IADL scale were seen among the participants before and after study.

It is worth noting that both studies [21,26] that demonstrated improvement in ADL were based on conventional TCM acupressure treatment contrasting to the less conventional approaches by Mariko et al. [22] (by touch) and Simoncini et al. [30] (by device). The ADL improvement could also be a cumulative effect after long-term acupressure treatment (6 months). As shown in Wan et al. [26], the mean ADL score of the treatment group, while improved, did not become statistically significant at the three-month point. Thus, the shorter treatment duration of Mariko et al. [22] (4 weeks) and Simoncini et al. [30] (8 weeks) might not long enough to demonstrate any significant effect in ADL. Besides, age and severity of dementia could also be the influencing factors. Wang and Kui [21] recruited a younger cohort and Wan et al. [26] recruited dementia patients living in community, and these factors could influence ADL. These are salient points to consider in future research.

3.4.5 Pain, anxiety, and mood

The study by Rodriguez-Mansilla et al. [23] had pain, anxiety, and depression as the primary outcome measures for assessing the effects of ear acupressure. This RCT recruited a total of 111 moderate to severe dementia patients and randomly assigned them into three groups: ear acupressure, massage, or control. Those who received ear acupressure had herbal seeds of Vaccaria fixed at three acupoints in the ear with adhesive tapes for three months. New seeds were replaced every 15 days for all participants in the group. The placements were checked daily with new ones affixed if the seeds had fallen. The massage group received massage treatment at the back and lower limbs for 20 minutes per day, five days a week, whereas the control group was under routine care only. Reactions to pain were recorded using Doloplus-2, a comprehensive tool for assessing behavioural pain in nonverbal elders. Depression was evaluated with the Cornell Scale for Depression in Dementia by assessors based on interviews with caregivers as well as direct observations. The study also measured anxiety level with Campbell scale that assesses the presence of anxiety or chronic pain in non-communicative persons [23]. Assessment of outcomes was carried out monthly for five months in this study. The study reported that the means of the control group for all measures deteriorated at all time points beyond the baseline and were significantly different ($p<.001$) from the other groups. Both intervention groups showed continual improvement in mean scores in pain, depression, and anxiety during the treatment duration (first three months). The mean scores deteriorated after treatment stopped and rebounded to the baseline level at the last time point. Ear acupressure was found to be more effective than massage treatment in reducing pain and depression with the changes from baseline significantly lower ($p<.05$) at all time points except the last. The mean anxiety score of the ear acupressure group was also significantly lower than that of the massage group at the fourth month.

Similarly, the observation study by Simoncini et al. [30] also found affixing an acupressure device at the Shenmen HT7 point for eight hours a day had

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effects on the psychiatric distress of the participants. The participants were administered with the 28-item General Health Questionnaire (GHQ-28), which assessed somatic symptoms, anxiety/sleep, depression, and social dysfunction. The study found a statistically significant improvement ($p<.001$) in the anxiety/sleep domain of GHQ-28 compared to baseline after completion of the acupressure treatment for two months [30]. However, measurements collected using another instrument for anxiety, namely the State-Trait Anxiety Inventory (STAI-Y1), did not detect any difference across time points, even though there was a positive trend of improvement [30].

Results from these studies [23,30] indicate that affixing acupressure device or herbal seeds on selected acupoints for an extended period may be potentially helpful in improving pain and depression, as well as anxiety to a certain extent, in dementia patients. At present, there is no clinical trial that evaluates explicitly the effect of the traditional form of body acupressure on pain, anxiety, and mood in dementia patients, which represents a gap in research.

3.4.6 Sleep

The primary objective of the study by Simoncini et al. [30] was to explore the effectiveness of acupressure for the treatment of insomnia and sleep disturbances in the dementia patients assessed with the Pittsburgh Sleep Quality Index (PSQI). PSQI is a self-rated questionnaire that assesses subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [42]. The study found that the perceived sleep duration of the participants improved significantly after treatment ($p<.001$) and maintained after four months ($p<.005$). Sleep duration was reported by every patient to increase after acupressure treatment, with an average between five to seven hours each night. The authors also commented that there was a decrease in sleep latency and an increase in subjective sleep for all patients after the 8-week treatment but did not provide supporting data. Overall, the mean total PSQI score decreased significantly ($p=.002$) from baseline to after treatment and maintained low at follow-up after four months [30].

There were major concerns in the study methodology and data interpretation of Simoncini et al. [30], as pointed out by Moran and Pedrera-Zamorano [43]. The study excluded participants who could not complete the self-administered PSQI due to deterioration in communication after baseline in data analysis. Such omissions resulted in high attrition rates in sleep data analysis which inevitably biased the findings. For statistical analysis, one-way ANOVA was used for dependent measurements, instead of repeated-measures ANOVA, without providing any justification that the data distribution fulfilled the required assumptions. Such severe methodological flaws rendered the reported results to be unreliable [43]. Thus, the evidence supporting the use of acupressure for improving sleep in dementia patients is still lacking.

3.4.7 Quality of life

Only one study attempted to evaluate health-related quality of life (QoL) as an outcome measure of acupressure for people with dementia. Wan et al. [26] used the 13-item QoL-AD scale to assess the QoL of each participant based on input from the patient, caregiver, and assessor. The mean QoL-AD rating for the acupressure group was observed to improve after three months of treatment and continued to increase favourably after six months. The mean difference between the measure at 6-month point and baseline was statistically significant. The changes in QoL correlated with improvement in cognition as measured by MMSE. No statistically significant change in QoL-AD scores was detected in the control group at all time points.

3.4.8 Ease of care

An ease-of-care inventory was developed in the pilot study by Yang et al. [29] to assess the subjective perception of ease of caring for dementia patients with a 5-point Likert scale (1= very difficult; 5= very easy). This inventory was administered three times to the nursing aides who took care of the participants during the

study with seven items of assessment: eating, toileting, bathing, grooming, sleeping, walking, and other activities. The mean ease-of-care rating was found to increase significantly (p<.001) from the pre-treatment to the post-treatment periods. After which, the mean ease-of-care score decreased following the 4-week control period.

The same ease-of-care inventory was also applied in the main RCT by Lin et al. [20] which evaluated the use of acupressure with Montessori-based activities in nursing home residents with dementia. In this cross-over study, the mean ease-of-care rating was found to improve significantly after the participants received acupressure (p<.001) and Montessori (p=.004) sessions but not during the control period with a mere physical presence.

It should be noted that the assessors of ease of care in both studies were nursing aides who were not blinded to the treatment received by the participants, hence the individual expectation might bias subjectivity in the assessment.

3.4.9 Biological markers

The early quasi-experiment study by Sutherland et al. [28] attempted to measure the waking-time pulse and respiratory rates of participants at every two hours during the 10-day treatment of foot massage and acupressure. The authors reported a decrease in means of pulse and respiratory rates following treatment, but the differences were not significant due to insufficient power.

Kwan et al. [31] explored the feasibility of using salivary cortisol as a measurement of stress for dementia patients under acupressure treatment. The pilot study reported statistically significant decreases in median salivary cortisol level among all the patients at week-1 and week-4 during the eight weeks of study. However, the study found an unsatisfactory yield of valid saliva samples due to hyposalivation in 53.33% of the participants. In the subsequent follow-up RCT, Kwan et al. [25,33] collected salivary samples four times (week 0, 3, 5, and 8) during the study. The study found a significant interaction between groups and time points, using a generalised estimating equation for data analysis, in the salivary cortisol level (χ^2 = 14.811, p=.022). After treatment, the acupressure group showed a significant reduction (p<.05) in the mean salivary cortisol level at week-3 and week-5, but not week-8, compared to the level at week-0. Significant reductions in salivary cortisol level were observed in neither the sham nor the usual-care groups. As such, two weeks of acupressure treatment appeared to lower the stress levels of the participants, and the effects sustained for even up to two weeks later. The study was also hampered by 54.8% missing data caused by hyposalivation, even though there were no significant differences in the number of missing saliva samples between groups and across different time points.

Yang et al. [24] used a heart rate variability (HRV) analyser to acquire, store and process the electrocardiogram signals of the participants in their RCT comparing aroma-acupressure to aromatherapy. The study used low-frequency percentage (LF%) and the ratio of low-frequency to high-frequency (LF/HF) to represent the sympathetic nervous activity. The high-frequency percentage (HF%) was used as an indicator of parasympathetic nervous activity. HRV data was collected at pre-treatment, weekly during the 4-week treatment, post-treatment, and three weeks post-treatment. The study found a weekly decline in LF% every week until the fourth week in the aroma-acupressure group. Significant differences in LF% (p<.01) and LF/HF (p<.04), compared to pre-treatment values, were detected in the fourth week. The HF in the aroma-acupressure group was also significantly higher (p<.01) in the second, third, and fourth weeks. In contrast, the aromatherapy group only exhibited significant differences (p<.01) in the second week for LF% and the fourth week for LF/HF. These results suggested that acupressure had added benefits over aromatherapy in promoting relaxation among dementia patients through switching the balance of nervous activities.

3.5 Summary of evidence

This review finds inconsistent evidence in the effectiveness of acupressure to reduce agitation

and behavioural disturbances among institutionalised dementia patients with BPSD, however, the treatment appears to improve their ease-of-care and reduce physical stress level as measured by salivary cortisol and HRV. Nevertheless, there is preliminary evidence suggesting that long-term (6 months) conventional TCM acupressure treatment can potentially improve the cognitive function, ADL, and QoL of patients with mild to moderate dementia. Affixing acupressure device on selected acupoints can also potentially improve psychiatric pain, anxiety, and depression among patients with moderate to severe dementia. Conversely, no good quality evidence supports acupressure treatment for sleep disturbances in the dementia population.

4 Discussion

The therapeutic effects of acupressure in older adults have been the subject of many recent systematic reviews (SRs). A meta-analysis of 18 studies by Chen et al. [44] found acupressure to be effective in improving sleep quality, cognitive functioning, and quality of life, as well as alleviating constipation and pain among older adults. A SR of 19 studies by Hmwe et al. [45] also found acupressure could improve sleep quality and possibly psychological wellbeing of older people. Acupressure was a promising non-pharmacological intervention for sleep improvement among nursing home residents, according to SRs by Shang et al. [46] and Capezuti et al. [47].

In the population with dementia, however, there is a lack of SRs that evaluate the beneficial effects of acupressure. Abraha et al. [16] classified acupressure as a form of sensory stimulation therapy in an SR of non-pharmacological interventions for BPSD. However, this SR included only one RCT that used acupressure in dementia participants and hence did not find the evidence to be convincing. Margenfeld et al. [17] considered acupressure as a form of manual massage for dementia patients. A total of 11 RCTs were included in this study, with four of them incorporating acupressure. The study found manual massage to have significantly beneficial effects over control in reducing anxiety ($p<.005$) and depression ($p<.00001$) among dementia patients, nevertheless, subgroup analysis of acupressure did not show significant group differences [17].

The scoping review by Harris et al. [48] is the only SR that focused specifically on the use of acutherapy for BPSD. The study, however, included not only acupressure (n=9) and but also acupuncture (n=6) studies in their analysis. Harris et al. [48] wrote that all included studies reported statistically significant improvements in agitation, depression, mood, and sleep with three-quarters of them reporting statistically significant improvements in ADL. Additionally, two-thirds of the studies reported statistically significant improvements in anxiety and neuropsychological disturbances. Nevertheless, the authors found comparison across studies and interpretations about effectiveness to be difficult due to variations in study design, intervention procedures, and outcomes [48].

The present study is the first to review the benefits of acupressure in people with dementia systematically and critically based on results from published clinical trials. Three additional studies [21,22,26] were included in addition to the nine previously reviewed by Harris et al. [48], among them were two studies published in Mandarin [21,26] that had never been assessed by any acupressure review published in English. Hence, this review offers the most comprehensive overview of the currently available evidence. Contrary to Harris et al. [49], this review did not find convincing evidence that acupressure has improved agitation, depression, mood, and sleep disturbance symptoms of BPSD. Notwithstanding, the authors reached the same conclusion with Harris et al. [49] that the heterogeneity across studies was too high and thus precluded any meaningful assessment of the effect size for any outcome measurement.

The present study has a couple of limitations. Firstly, the search strategy was limited to major databases with English keywords and abstracts only. Since most included studies were originated from the Greater China region, a future review with more exhaustive searches using major Chinese databases to uncover Chinese language

publication in this topic is warranted. Secondly, due to the lack of time and resources, the authors only assessed the available evidence qualitative without adhering to any rigorous methodology. Further study should adopt a systematic approach, such as one based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system [49] or OCEBM (Oxford Centre for Evidence-based Medicine) Levels of Evidence [50] to rate the quality of evidence and provide grading for any clinical recommendation.

5 Conclusion

Acupressure is a non-pharmacotherapy that can be beneficial to patients with dementia of all levels of severity. While the available research evidence is promising, the effects of acupressure on different manifestations of BPSD remain unclear. More high-quality RCTs are needed to fill the gaps in knowledge and inform better care for dementia patients in the future.

Author contribution

GD and SLO conducted the literature search and data synthesis. SCP supervised the project. GD prepared the initial draft. SLO conceived and wrote the review. All authors reviewed and substantially contributed to the final version of the manuscript.

Financial support

All authors declared that no financial support was received from any organization for the submitted work.

Conflicting Interests

The authors declared that there is no conflict of interest.

Acknowledgement

The authors thank the staff support from Charles Sturt University Library and Research Office.

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Figure 1 Literature search flow diagram.

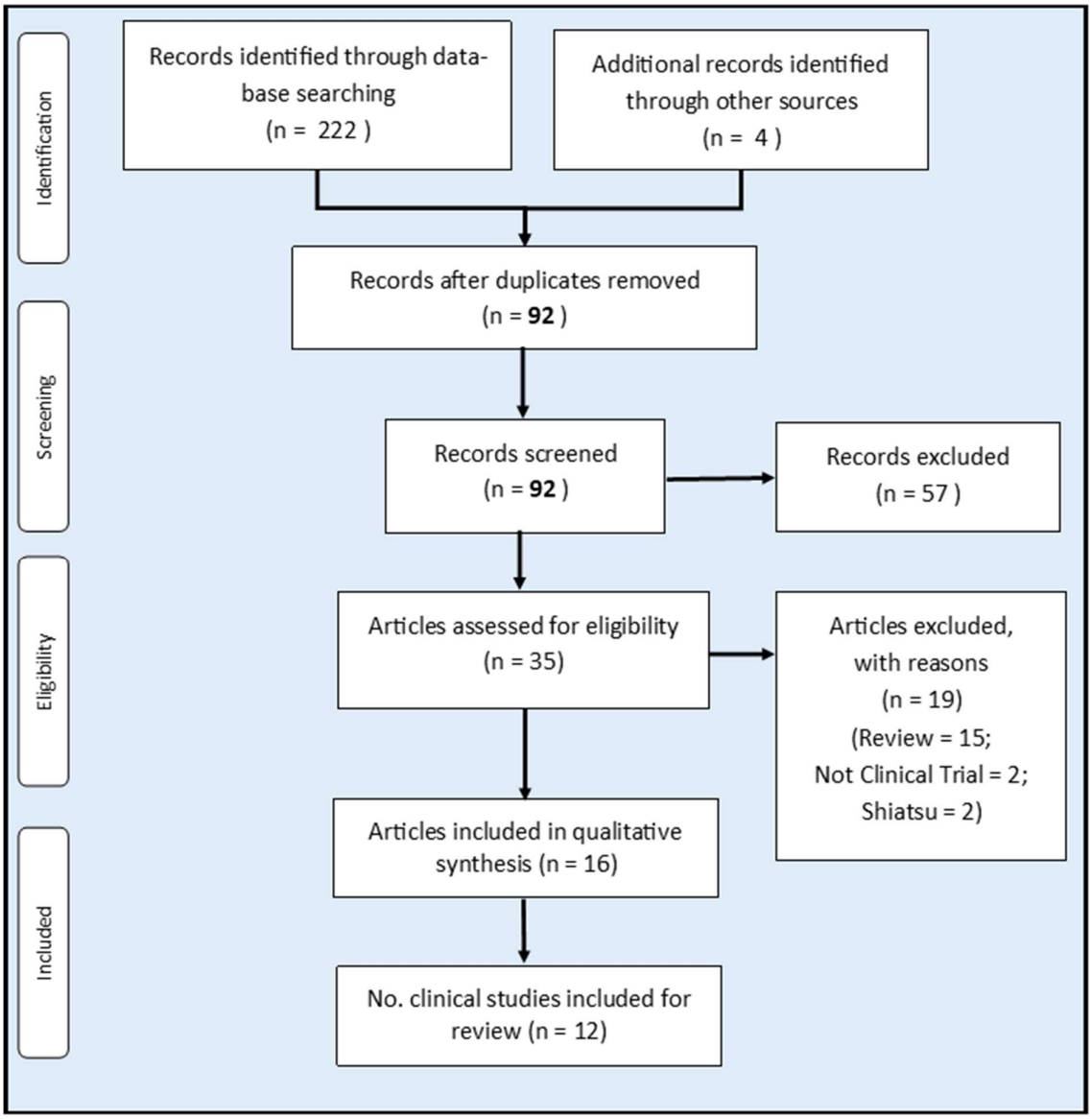

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Table 1. Summary of randomised controlled trials investigating the effects of acupressure in dementia patients.

Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings
Lin et al. (2009) [20] Taiwan	Multi-site, assessor-blinded, randomised, active & passive-controlled, cross-over trial.	Institutionalised dementia patients (6 sites) with CMAI score ≥35. N=133, 3 cross-over groups (seq. 1, n=42; seq. 2, n=39; seq. 3, n=52).	All groups received acupressure (5 acupoints, 2min/point plus warm-up for 15 min total), Montessori methods, and presence in different sequences. Treatment period: 4 weeks per sequence (1x/day, 6 days/week). Study duration: 22 weeks.	Agitation (CMAI), ease-of-care rating, emotional response (AARS), frequency of family visits, restrain use, before and after each treatment sequence.	Compared to presence, acupressure and Montessori-methods significantly decreased overall agitated behaviours (p=.001), aggressive behaviours (p=.001), physically nonaggressive behaviours (p=.02), and improved ease-of-care ratings (p≤.004). Only Montessori-methods significantly invoked positive affect compared to the controlled presence (p=.02).
Wang & Kui (2014) [21] China	Single-site, randomised, passive-controlled, parallel trial	Patients diagnosed with AD (CCMD III-R). N=78, acupressure (n=39) and control (n=39).	The control group received routine care only. The acupressure group received additional acupressure treatment (6 acupoints, 60x/point plus ear massage) 2x/day (AM, PM). Treatment & study period: 6 months.	Barthel Index for ADL, before and after treatment.	More participants in the acupressure group attained better ADL grading after treatment than those in the control group. The between-group difference was statistically significant (p <.05).
Mariko et al. (2015) [22] Japan	Single-site, assessor-blinded, randomised, passive-controlled, parallel trial.	Institutionalised long-term care patients diagnosed with AD (DSM-IV). N=23, touch (n=11), control (n=12).	The touch group received acupressure (gentle touch on the Shenzhu acupoint with palm for 3 min over clothes), 2x/day (AM, PM). Control group received routine care only. Treatment & study period: 4 weeks.	Neuropsychological disturbances assessed with NPI, MMSE for cognitive function, and Barthel Index for ADL, before and after treatment.	Post-treatment, NPI decreased significantly in the touch group but not in the control group (p <.05). No significant changes in the MMSE scores and the Barthel Index for both groups.

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Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings
Rodríguez-Mansilla et al. (2015) [23] Spain	Single-site, patient & assessor-blinded, randomised, active & passive-controlled, parallel trial.	Institutionalised patients with moderate to severe (MMSE: 0-20) dementia (DSM-IV). N=111, massage (n=35), acupressure (n=40), control (n=36).	The acupressure group had herbal seeds of Vaccaria placed with adhesive tape at 3 ear acupoints. Back and lower limbs massage for the massage group (20min/day, 5 days/week). The control group received routine care only. Treatment period: 3 months. Study duration: 5 months.	Cognitive deficits (GDS), cognitive function (MMSE), behavioural pain (Doloplus-2), depression (CSDD), anxiety/pain (Campbell scale), measured at 6 monthly time points.	Both acupressure and massage group consistently exhibited significantly better averages ($p<.001$) in all outcome measures from baseline compared to control. The acupressure group showed significantly better improvements ($p<.05$) in pain and depression than the massage group during the treatment period and at one month of follow-up.
Yang et al. (2015) [24] Taiwan	Multi-site, assessor-blinded, cluster-randomised, active & passive-controlled, parallel trial.	Institutionalised dementia (DSM-IV) patients (6 sites) with CMAI score ≥35. N=186, aroma-acupressure (n=56), aromatherapy (n=73), control (n=57).	Interventions were aroma-acupressure (pressured with lavender oil at 5 acupoints, 2 min/point plus warm-up for 15 min total) or aromatherapy (applied lavender oil at the same 5 acupoints for 15 min with no pressure). The control group received routine care only. Treatment period: 4 weeks (1x/day, 5 days/week). Study duration: 7 weeks.	Agitation assessed with CMAI and HRV at pre-, post-, and post-3-week intervals. Additional HRV tested weekly during the intervention period.	Both the aroma-acupressure and aromatherapy groups experienced significant improvement ($p<.001$) in agitation at post-test and post-3-week compared to no significant change observed in control. HRV analysis showed parasympathetic nervous activity increased from the 2nd week to the 4th week in the aroma-acupressure group and in the 4th week in the aromatherapy group
Kwan et al. (2017) [25] Hong Kong	Multi-site, patient & assessor-blinded, randomised,	Institutionalised dementia patients (12 sites) fulfilled the CMAI criteria of agitation for ≥1 month.	Acupressure (5 acupoints pressed in 3 steps, 3min/step for 9 min total) or sham (5 non-acupoints pressed in 3 steps, 3min/step for 9 min total). The	Agitation assessed with CMAI, stress level measured with salivary cortisol concentration, in 4 time points (pre-,	Acupressure has no significant effect on reducing agitation compared to sham or control. A significant reduction in cortisol was seen in the acupressure group

Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings
	active & passive-controlled, parallel trial.	N=119, acupressure (n=39), sham (n=41), control (n=39).	control group received routine care only. Treatment period: 2 weeks (2x/day, 5 days/week). Study duration: 8 weeks.	post-, post-3-week, post-6-week).	compared to the control groups with the effect size of 1.04 (Cohen's d).
Wan et al. (2017) [26] China	Single-site, randomised, passive-controlled, parallel trial.	Community dementia (DSM-V) patients with permanent carers. N=80, acupressure (n=38), control (n-40).	The control group received routine care only. The acupressure group received additional acupressure treatment (6 acupoints, 3 min/point plus ear, thumb, and toe massage) 2x/day (AM, PM). Treatment & study period: 6 months.	The severity of dementia (HDS), cognitive function (MMSE), ability to perform ADL, and QoL-AD, assessed before and after treatment.	The scores of HDS, MMSE, ADL, and QoL-AD in the acupressure group were significantly higher compared to baseline and that of the control group ($p<.05$), indicating better symptom control.
Fung & Tsang (2018) [27] Hong Kong	Multi-site, randomised, active-controlled, parallel trial.	Institutionalised dementia patients (3 sites) with MMSE <20 and reported having BPSD. N=60 in 3 groups (n=20 each)	Group 1: aroma-massage with acupressure + exercise. Group 2: cognitive training + exercise. Group 3: aroma-massage with acupressure + cognitive training. Used standardised aroma-massage (lavender oil) with acupressure protocol covering 9 acupoints (max 20min including warm-up). Treatment period: 3 weeks (2x/week). Study duration: 4 months.	CMAI for agitation, NPI for neuropsychological disturbances, and MMSE for cognitive function at pre-, post-, and post-3-month timepoints.	CMAI scores of all groups at all time points were not significantly different. Group 1 and 3 participants showed a significant reduction ($p=.04$) in the severity and distress scores of NPI.

Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings

Legend: AARS, Apparent Affect Rating Scale; AD, Alzheimer's disease; ADL, activities of daily living; BPSD, behavioural and psychological symptoms of dementia; CCMD, Chinese Classification of Mental Disorders; CMAI, Cohen-Mansfield Agitation Inventory; CSDD, Cornell Scale for Depression in Dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Global Deterioration Scale; HDS, Hasegawa's Dementia Scale; HRV, heart rate variability index; MMSE, mini-mental state examination; NPI, Neuropsychiatric Inventory; QoL-AD, Quality of Life - Alzheimer's disease.

Table 2. Summary of quasi-experimental studies on the effects of acupressure in dementia patients.

Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings
Sutherland et al. (1999) [28] USA	Site-site, purposive sampling, random assignment, passive-controlled, parallel trial.	Institutionalised AD patients requiring behavioural management. N=10, acupressure (n=5), control (n=5).	The control group received routine care only. The acupressure group received additional 10 min foot massage plus acupressure treatment (4 acupoints, 5 min/foot, 1x/day). Treatment period: 10 days. Study duration: 13 days.	A custom-designed BDI for behavioural assessment was done every 2 hours during the entire study.	Post-treatment means showed a decrease in wandering, pulse, and respiration, and an increase in quiet time. The changes in scores were not statistically significant.
Yang et al. (2007) [29] Taiwan	Site-site, passive-controlled, cross-over trial.	Institutionalised dementia (DSM-IV) patients with CMAI score ≥40. N=20.	All participants received acupressure (5 acupoints, 2 min/point plus warm-up for 15 min total) in the first period followed with a visiting and conversation period as a control. Treatment period: 2x 4 weeks (2x/day, 5 days/week). Study duration: 13 weeks.	Agitation assessed with CMAI and Ease-of-Care rating at before and after each period. Agitated behaviours were recorded daily.	CMAI scores decreased significantly after acupressure intervention ($p<.001$) and increased after the control period. The post-test CMAI scores for the acupressure and control phases were significantly different ($p<.001$) across all domains.
Simoncini et al. (2015) [30] Italy	Multi-site, longitudinal prospective study	Institutionalised AD (NINCDS-ADRDA) patients (2 sites) with mild cognitive impairment (GDS level 0-3) who suffered from insomnia or sleep disturbances.	Acupressure was administered on HT7 acupoints on both wrists for 8 hours/day by affixing a specialised device. Treatment period: 8 weeks. Study duration: 6 months.	Dementia symptoms assessment with MMSE, GDS, NPI, STAI-Y1, ADL, and IADL; Psychiatric distress measured with GHQ-28, and perception of sleep with PSQI. Measurements were done	Statistically improvement in sleep, mood, and cognitive function were detected with mean scores of GHQ28 ($p=.003$), PSQI ($p=.002$), NPI ($p<.001$) at post-treatment and 4 months after, compared to baseline. The use of sedative drugs also significantly reduced ($p<.001$).

Study	Study Design	Participants	Interventions	Outcome Measures	Efficacy Findings
		N=129.		at baseline, post-treatment, and 4 months post-treatment.	
Kwan et al. (2016) [31] Hong Kong	Multi-site, time series design	Institutionalised dementia patients (3 sites) fulfilled the CMAI criteria of agitation for ⩾1 month. N=24, allocated into 8 groups (n=3 each).	Different group received acupressure (5 acupoints pressed in 3 steps, 3min/step for 9 min total) in different frequency (1x or 2x/day) and treatment period (1,2,3, or 4 weeks). Study duration: 8 weeks	Agitation was measured by CMAI, stress by salivary cortisol level. Measurements were done weekly.	The reduction of median CMAIs was significant ($p<.001$) at weeks 1, 4, 5, and 6 compare to baseline. The reduction in median salivary cortisol level was significant in weeks 1 ($p = .011$) and 4 ($p = 0.01$). Acupressure had the largest effect when performed twice a day ($p=.026$) for 2 weeks ($p=.005$).

Legend: AD, Alzheimer's disease; BDI, Behavioural Documentation Instrument; ADL, activities of daily living; CMAI, Cohen-Mansfield Agitation Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Global Deterioration Scale; GHQ, Global Health Questionnaire; IADL, instrumental activity daily living; MMSE, mini-mental state examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; PSQI, Pittsburgh Sleep Quality Index; STAI, State-Trait Anxiety Inventory.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2021 doi:10.20944/preprints202108.0532.v1

Table 3. Summary of acupoints used in the included clinical trials

Location	Point Name	Reference	Total Trials
Head	Baihui	GV20	8 [20,21,24–27,29,31]
Arm	Shenmen	HT7	7 [20,24,25,27,29–31]
Head	Fengchi	GB20	6 [20,24–26,29,31]
Arm	Neiguan	PC6	6 [20,24,25,27,29,31]
Leg	Sanyinjiao	SP6	4 [20,24,27,29]
Head	Yingtang	EX-HN3	3 [25,27,31]
Head	Taiyang	EX-HN5	2 [26,27]
Head	Shenting	GV24	2 [26,27]
Head	Sishencong	EX-HN1	2 [21,26]
Arm	Lingdao	HT4	1 [27]
Arm	Tongli	HT5	1 [27]
Ear	Myorelaxant	159.C	1 [23]
Ear	Ear - Heart	MA-1C	1 [23]
Ear	Ear - Shenmen	MA-TF1	1 [23]
Back	Shenzhu	GV12	1 [22]
Leg	Xuanzhong	GB39	1 [21]
Leg	Taixi	KD3	1 [21]
Leg	Dazhong	KD4	1 [21]
Leg	Zusanli	ST36	1 [21]