

Review Article

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Acupuncture for Chronic Stress: A Systematic Review

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ABSTRACT

Objective: The growth in instances of illness related to chronic stress nowadays is worrying, and relevant treatment is vital, and safe therapies with no side effects, like acupuncture, are being sought more and more. This study intends to identify and outline the evidence available from randomized clinical trials, as well as systematic reviews, with the objective to test the efficacy of acupuncture in the treatment of chronic stress. It is also our purpose to identify the mechanics behind the use of acupuncture for this purpose and, in this way, contribute to a better understanding and acceptance of this complementary therapy.

Method: Research has been carried out within the databases of both Pubmed and Cochrane for articles published between 2011 and 2021. The terms used were acupuncture and chronic stress.

Results: 53 studies were found through Pubmed and 66 through Cochrane, and from these, 6 were selected and analyzed.

Conclusion: The potential mechanism involved in the response to treatment has been identified. However, the studies selected and analyzed were not sufficient to prove evidence that acupuncture is effective in the treatment for chronic stress.

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Introduction

According to data from the Direção Geral da Saúde (DGS), Mental Health in numbers and the National Mental Health Epidemiological Study of 2013 by the Medical Science Faculty, Nova Medical School, more than a fifth of the Portuguese population suffers from a psychiatric disorder [1,2]. Portugal has the second highest incidence rate within the European Union, with 16.5% of Portuguese suffering from anxiety disorders and 7.9% from mood disorders. These disorders are also one of the main causes of morbidity and disability [3]. Cardiovascular diseases are still the main cause of death with stress as one of their major risk factors.

In 2019, stress was recognized as a worldwide pandemic by the World Health Organization (WHO), bringing awareness to its devastating effects [4]. Therefore, the treatment and prevention of stress must be a priority, especially given the recent Covid19 pandemic (which began in December 2019).

Therapies and stress-targeted coping mechanisms have been developed through the course of time, as well as the search for solutions that are safe and don't require medication. Acupuncture has risen in popularity as fitting both of these requirements, and in light of existing knowledge on the pathophysiology of stress

and the mechanics behind acupuncture, it is considered relevant to investigate the results of studies made with regard to this subject. This article intends to synthesize results from the last 10 years about the efficacy of acupuncture in the treatment of chronic stress and to contribute to the knowledge in this area, promoting it as a treatment based in current evidence.

State of Art

Stress constitutes an organic response to stimuli (physical, psychic, or social), which is perceived as a threat to homeostasis or wellbeing. The response to this threat may be fight, flight or inaction, so that the stimulus can be processed, and a reaction provided, with several factors coming into play. It is a physiological and behavioral response which promotes the organism's coping mechanisms [5]. The autonomous nervous system is activated, specifically the sympathetic nervous system (SNS) which increases the circulation of glucocorticoids. In the hypothalamus, the paraventricular nucleus neurons release the corticotrophin releasing hormone (CRH) which, in turn, adrenocorticotrophin hormone (ACTH). The ACTH stimulates the adrenal cortex into producing cortisol [6]. When the threat has passed or has been resolved, this system will disconnect in the form of a negative feedback response.

Only when the stress-causing stimulus continues and extends in time will the organism enter in exhaustion, being unable to respond adequately – and this is what constitutes chronic stress.

The Hypothalamic–pituitary–adrenal axis (HPA) is no longer able to respond adequately which leads to a rise in CRH, of arginine vasopressin (AVP), which increases the production of ACTH, rising the PVN neurons reactive input, modifying the GABA receptor expression and that of glutamate in these same neurons, reducing the negative feedback (promotor of homeostasis) [6].

The restrictions of these negative feedback mechanisms occur especially in the limbic area which controls emotional responses and humor. There is also a disruption in cellular and systemic equilibrium, which causes disfunction in the nervous and organic peripheral systems. This is what justifies that the condition of prolonged traumatic or psychological stress can, for instance, cause alterations and other dysfunctions in internal systems which control the response to stress and the occurrence of neurological and psychosomatic illnesses. This supports the reports of psychological stress and systemic diseases both being associated with adverse effects on mental health and with the occurrence of psychiatric illnesses, for example, in the bipolar disorder, post-traumatic stress like comorbidity [7]. When comparing data on the prevalence of depression, it is seen that 50% of patients with systemic chronic illness (pain, stroke, cardiovascular disease, diabetes, cancer) suffer from depression whereas in the general population, depression is present in about 5 to 8% [8].

Recent studies show that the immune-inflammatory system is the key to the complex interaction of stress and illness, with inflammation being involved in all chronic illnesses, as well as in the process of ageing [8,9]. Chronic stress is one of the major risk factors for the development of pathologies of the psychological realm, such as post-traumatic stress and depression. Chronic stress, by way of the endocrine system, affects the brain's structure, immune response, behavior and, our epigenetic, being associated with the elevation of blood pressure, elevation of glucose in plasma, the metabolic syndrome, obesity and cancer [6,10]. It is therefore associated to several mental disorders (post-traumatic stress, major depression, bipolar disorder, schizophrenia, anxiety disorders and addiction), cardiovascular diseases and a multitude of other pathologies, be that as the cause or exacerbating factor [11]. The exposure to chronic stress and its development are directly associated with common psychopathology [12].

The exposure to chronic stress also increases the chances of cardiovascular disease, psychiatric and metabolic diseases. Psychosocial chronic stress even predicts the likelihood of cardiovascular disease, morbidity and cardiovascular mortality and doubles the risk of myocardial infarction [5]. Chronic stress is an independent risk factor to atherosclerosis. Where there is chronic stress, cortisol and the catecholamines that regulate blood pressure and circulation can lead to endothelium injury, perforation of platelets and the proliferation of hematopoietic stem cells. Aside from that, the overstimulation of the sympathetic system promotes the release of catecholamines, provokes the contraction of the coronary artery but also the rupture of atheroma plaques, simultaneously there is a rise in pro-inflammatory cytokines, in the expression of adhesion molecules which, through certain routes can induce the aggregation of mononuclear cells and lymphocytes. Lipid metabolism imbalance altered epigenetic patterns, depression, macrophage activation and lipid formation (involved in the forming of the atheroma plaque) are also associated with chronic stress [13]. Consequently, chronic stress is a disorder that can cause both pathophysiological changes, as well as a surge in diverse pathologies.

Stress can lead to risk behaviors, such as smoking, drinking alcohol, overeating and even addiction. However, there is a growing mentality that supports healthier strategies and therapies to assist in handling stress more effectively. WHO shared a guide in 2020 with an emphasis in the importance of stress: *Doing what Matters in Times of Stress: An illustrated guide for coping with adversity*, a simple guide to be consulted by any citizen and available in several languages [14]. In American Psychological Association's report, *Stress in America de 2017* healthier strategies to deal with stress are described, including listening to music (47%), walking/exercising (46%), praying (29%) and meditating/yoga (12%) [15]. There is an increasing search for healthy solutions, and there is also an increase of confidence in the efficacy of psychology in the treatment of stress (42% confidence in 2017 as opposed to 38% in 2016).

Acupuncture is one of the treatment possibilities in this context [16]. Acupuncture is a millenary treatment within Traditional Chinese Medicine (TCM). TCM originated about 3000yearsago in China. It then expanded to the West with the first scientific publications from the 19th century [16]. Acupuncture has known a development in the understanding of its scientific mechanisms since the 70s, with more than 80000 published articles. It is currently practiced all over the world as a Complementary Therapy, having been recognized by WHO in 1997, having even been added to their 2019 diagnostic manual [17].

This technique consists in the insertion of fine needles in specific points on the meridians (similar to a circulatory system of energy - Qi) along the body. Its purpose is the promotion of correct energy circulation, promoting homeostasis [18]. It has been one of the most studied and documented therapeutic modalities. Its effects are explained by several mechanisms. The stimulation, through Acupuncture, of the nervous fibers in muscles, fascias, tendons, periarticular and, osseous tissue, sends impulses to the spinal marrow and activates several centers of the brain which release neurotransmitters promoting homeostasis; it modulates neural activity in the diencephalon which, in turn, impacts on the autonomous, endocrine and, immune functions through the HPA, which regulate the circadian release of ACTH, vasopressin and cortisol, producing homeostasis.

In TCM, an illness is seen as an energetic imbalance with internal or external causes. Stress, when produced by emotions, fits into the internal causes of illness. Its treatment and/or prevention fits into the quadrant of mental health which, for TCM cannot be separated from physical health. In any treatment protocol there are always acupuncture points for emotions and mental health [19]. In light of TCM theory, each emotion is associated to an organ, which in turn also corresponds to a specific tissue. Stress caused by fear affects the Kidneys primarily. The bones are the corresponding tissue [20]. This theory was partially corroborated recently in the study of Berger et al, which connects the Osteocalcin hormone produced by bones in response to acute stress [21].

Materials and Methods

Seeing as these articles was meant as a revision of current literature with the objective of researching the level of evidence in the effectiveness of using acupuncture to treat chronic treatment, the study materials were scientific articles published in magazines archived in internationally accredited systems.

Strategy used to identify relevant studies: there search was done in 2 databases, Pubmed and Cochrane Library. The research strategy considered the terms 'acupuncture' and 'chronic stress'.

The research was completed by the end of March 2021, having initially found 119 publications.

Inclusion Criteria: As inclusion criteria, the articles selected where those where the theme considered both the research terms: 'acupuncture' and 'chronic stress'; articles of the type: clinical trial, meta-analysis, randomized clinical trial, revision, and systemic revision; studies published in the last 10 years, in English language.

Exclusion Criteria: books and other documents were excluded.

119 articles were identified in the two databases selected for this study: 53 in Medline via PubMed and 66 in Cochrane Library. After the initial analysis, only 6 articles fit into the eligibility criteria. Figure 1 presents the flowchart for the selection process for articles included in this research (Figure 1).

Of those included, two are systematic revision articles, one Korean and another Chinese; four articles are randomized clinical trials, of these three are English and one is German (Table 1).

Results

Article 1

In the study by Huang et al, 18 participants were randomly selected and split into 3 groups [23]. The first group were treated with acupuncture, the second were given attention/relaxation and the third were the control group (without intervention). Acupuncture treatments were individually targeted and not following a specific protocol. The study was conducted over the course of 5 weeks, one 45-minute session per week. At the end of those 5 weeks, a focus group was gathered to attain the experiences and expectations of the treatments used. With regard to results, the largest difference between 2 groups was the experience reported by the participants in the stress related intervention. Some individuals from the acupuncture group felt less stress after treatment, with colleagues and family members noticing that they were more relaxed after the treatment. One individual also reported improvement in a stress related symptom he suffered. In the attention group, none of the participants reported improvements in their symptoms, neither positive feedback from colleagues nor family. However, all of the participants felt the benefits of relaxing and lying down.

Article 2

In the study by Huang et al, 18 participants with chronic stress were randomly divided into three groups with 6 participants [24]. The first group was treated with acupuncture, the second with attention and, the third without anything, as control group. In the group treated with acupuncture, participants had weekly sessions that lasted 45 minutes, over the course of 5 weeks (see protocol in table 2). The attention group had sessions of the same duration and frequency as those in the acupuncture group. Participants laid down on a couch and had appointments with a therapist who just asked questions and took notes. In the control group no intervention took place. In this study, Perceived Stress Scale (PSS-14) and Measure Yourself Medical Outcome Profile (MYMOP) forms were used to determine stress levels and the self-perception of health and wellbeing, before and after intervention [25]. The results showed that participants in the acupuncture group improved significantly when compared to the other 2 groups, even in other

symptoms such as tiredness, anxiety, insomnia and, rage. One of the participants who suffered from amenorrhea menstruated again. In the attention group, no specific symptoms improved, although scores improved in the MYMOP. The results from the control group showed worsening scores on both the PSS-14 and the MYMOP but of no statistical significance. The authors related these results (those of the control group) to the Hawthorne effect, which explains that differences may exist in study results as a consequence of individuals changing their patterns of behavior when they know they are being observed [26].

Article 3

In the study by Huang et al, 18 participants suffering from stress, with a score of 20 or more in the PSS-14, were randomly split into three groups [27]. One being treated with acupuncture (see protocol in table 2) the second with just attention and the third as the control group (no intervention). A PSS-14 was done at the beginning (baseline), at the end and, after 2 weeks (follow up). Saliva samples were collected in 9 separate days over the course of 8 weeks from all three groups. On each testing day, 4 samples were taken, one when they woke up, one 30 minutes after waking up, one 3 hours after waking up and the last 12 hours after waking up. After the end of the intervention, the PSS-14 score improved in all groups: 13, 9% in the acupuncture group, 18, 9% in the attention group and only 3, 8% in the control group. The differences were not statistically relevant. The acupuncture and attention groups showed an increase in cortisol in the morning (which signifies improvement in the pattern), whilst the control group showed a decrease in cortisol in the morning (associated to a pattern of worsening stress).

Article 4

In the study by Wild et al, 70 participants were randomly split into three groups [28]. The first group were treated with acupuncture, the second with Sham acupuncture and the third was the control group (see protocol in table 2). The primary tool for evaluation was the Perceived Stress questionnaire (PSQ-20) which measures perception and evaluates how stress stimuli are processed to which was added the stress module from the Patient Health Questionnaire and the Generalized Anxiety Disorder Scale (GAD 7) Levels of cortisone and cortisol concentration were measured in the first urine of the day [29-31]. An initial evaluation was done (baseline), after the end of the treatments or of the wait (in the case of the control group) and three months after the end of treatments (follow up). In these evaluations, participants filled out a questionnaire and gave samples of blood and urine. Cardiac pressure was also registered. The results demonstrated that acupuncture had a positive effect on stress reduction ($p < 0,05$) as well as in the associated parameters when compared to the control group. With regard to the comparison between acupuncture and Sham, results indicate that the first may be the most effective.

Article 5

In the study of the revision by Roh et al., the effects of acupuncture on addition-related stress were evaluated [32]. It was concluded that acupuncture reduces the response to stress through various mechanisms. Studies on mice (included) demonstrated that these mechanisms include the inhibition of the sympathetic-adrenal medullary system (exposed to paralyzing stress), inhibition of the HPA system (in maternal separation) and in the suppression of the HPA system (in the ethanol detox). Other studies have shown that acupuncture suppresses neural activity of CRH in the amygdala and in various other regions of the brain. Acupuncture can activate neural pathways, improving the efficacy of homeostatic stress-

coping mechanisms and of recompense in the brain, which in turn reduces levels of anxiety and symptoms related to stress.

Article 6

In the study of the revision of Han et al, the effects of electroacupuncture (EA) in the treatment of depression were being evaluated [18]. This study concluded that chronic stress causes an abnormal expression of genes and that this expression aggravates psychological disorders, originating a vicious circle which interferes in the treatment of depression. With EA as the treatment, gene expression normalized in 8 genes related to depression. EA possesses various therapeutic mechanisms: inhibition of hyperactivity of the HPA axis, increase in the expression of the neurotrophic factor derived from the brain (BDNF), regulation of neuropeptides and neurotransmitters, promotion of pathway signs, modulation of the expression of some genes, reduction of pro-inflammatory cytokines and the restoration of synaptic elasticity in the hippocampus. It's important to mention that no side effects were reported with regard to the intervention by acupuncture. The safety of acupuncture has been widely tested making it one of its advantages (Table 2: Summary of the articles from Randomized/ Controlled Studies) [33].

Discussion

One of the objectives for this revision article was to evaluate acupuncture's mechanisms. This was obtained through the two revision studies included which report the physiologic mechanisms that explain the positive effects of acupuncture in the treatment of depression and addiction (in which chronic stress is implied in the genesis and/or worsening of these pathologies).

Article 4 had a larger sample (n=70) than the remaining studies (n=18) and it was the only one to run a statistical analysis with an outrightly positive outcome ($p<0,05$). However, we cannot consider this result significant seeing as the randomized groups had a sample inferior to 30 participants.

Seeing as none of the studies obtained statistically significant results, although all of them showed good results in the groups with acupuncture as the treatment, it would be best to run studies with larger samples and measure their results statistically so that safer conclusions can be drawn on a final analysis.

It must be noted that none of the studies was designed to include acupuncture as complimentary to another therapy. It was only compared to attention groups (with relaxation), control groups (without intervention) and, in one case, with a sham acupuncture group. Its effectiveness was considered superior when compared to the other groups. The period of intervention may have been short, 5 weeks in three of the studies and 3 months in another one. One of the studies doesn't mention what protocol (of acupuncture) was followed whilst the 2 others followed the same protocol to which other points were added according to the differential diagnosis. One of the studies also considered the improvement in other symptoms such as insomnia, anxiety, anger, and tiredness.

Due to their heterogeneity, it is difficult to draw clear and definitive conclusions. This is one of the challenges of acupuncture and TCM. Its treatment depends on a differential diagnosis and on the choice of which points to use which will vary greatly from patient to patient.

Evaluation methods included filling out questionnaires (PSQ-20, PSS 14, GAD7 and the MYMOP), collecting blood and saliva samples for cortisol and cortisone, as well as, measuring patient's

heart rate. The variety in these methods was meant to measure in the most correct and extensive way the effects of acupuncture, leading to the most accurate results as possible.

The interpretations of acupuncture mechanisms can explain the positive results in the chosen studies. These include the modulation of the organism's response to stress at different levels, from the elasticity of the hippocampus to the HPA axis in the modulation of the inflammatory response, hormonal response and the genes' expression resulting in the promotion of homeostasis. Since the mechanisms involved in explaining its positive action with regard to chronic stress are multiple, its comprehension and evaluation becomes difficult.

Conclusions

Although the results of studies in the last 10 years, present in Pubmed and Cochrane with regard to the efficacy of acupuncture in the treatment of chronic stress, are not statistically relevant, we can conclude that:

- There is evidence of acupuncture being an important weapon in the fight against chronic stress and associated symptomatology, and going as far as to prevent the development of numerous pathologies;
- When performed by qualified professionals, acupuncture is a safe therapeutical tool, free of side effects; - The action mechanisms involved can explain the positive effects of acupuncture;
- It is necessary to conduct more and better designed studies, with larger samples and longer duration, so as to be able to draw statistically significant conclusions.

Authors' Contribution

F.Baião wrote the manuscript. E.Sampaio and M.Faria revised the final manuscript.

Registration

The review was not registered.

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Competing Interests

Authors state no conflict of interest.

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