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# REVIEW

# Has acupuncture benefit in the management of migraine? A scoping review



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#### **KEYWORDS** Acupuncture;

Chinese traditional

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## Abstract Introduct

Introduction: Migraine is the most common cause of primary headache, affecting over 1 billion people worldwide, but the high burden of this pathology along with the lack of effective therapies have allowed the implementation of alternative therapies like acupuncture for managing this condition. *Objective:* To evaluate the impact and effectiveness of acupuncture in the management of migraine with or without aura based on scientific literature available until May 27, 2021. *Materials and methods:* Scoping review that include Pubmed, SCOPUS and 18 databases of the World Health Organization International Registry of Clinical Trials Platforms. Theoretical publications and clinical trials in English, Spanish and French were included. *Results:* 84 documents and 62 clinical trials were included, where they evaluate acupuncture in settings of acute migraine attacks, as chronic prophylaxis in migraine and compared with drugs available for prophylaxis. *Conclusion:* Acupuncture is a safe, effective and cost-effective therapy in the management of acute migraine attacks and as prophylaxis for chronic migraine.

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PALABRAS CLAVE Acupuntura; migraña; medicina tradicional china; revisión exploratoria; revisión sistemática ¿Tiene la acupuntura beneficios en el manejo de la migraña? Una revision exploratoria

#### Resumen

*Introducción:* La migraña es una de las causas primarias de cefalea, afectando a más de un billón de personas a nivel mundial, pero, la alta carga de morbilidad de esta patología junto con la limitada efectividad de terapias ha llevado a la implementación de terapias como la acupuntura para su manejo.

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*Objetivo*: Evaluar el impacto y efectividad de la acupuntura en el manejo de la migraña con o sin aura con base en una revisión de la literatura científica disponible hasta mayo 27 de 2021. *Materiales y métodos*: Revisión sistemática exploratoria que incluyó las bases de datos Pubmed,

SCOPUS y 18 bases de estudios clínicos de la Organización Mundial de la Salud. Fueron incluidas publicaciones teóricas y ensayos clínicos cuyo idioma fuese español, inglés o francés.

*Resultados*: Se incluyeron 84 documentos y 62 ensayos clínicos, donde la acupuntura fue evaluada en ataques agudos de migraña y como profilaxis para la migraña crónica, además, fue comparada con las medicaciones disponibles.

*Conclusión*: La acupuntura es una terapia segura, efectiva y costo-efectiva en el manejo tanto en los ataques agudos de migraña como profilaxis para la migraña crónica.

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#### Introduction

Migraine is a chronic illness that can range from moderate to severe - and might be disabling. According to the Global Burden of Disease Study 2016,<sup>1</sup> it affects 1000 million people, locating this pathology as the second cause of disability worldwide. This condition has a complex pathophysiology, because it is an addition between genetic, epigenetic, and individual factors. Genetics have become a research point based on investigation findings, including a high penetrance, that can reach up to 70%,<sup>2</sup> also, there is genetic susceptibility, showed by the rate of this condition in monozygotic twins,<sup>3</sup> and, most recently, the work made by Gormely et al.<sup>4</sup> shows 38 different loci related with migraine, most of them affecting muscular and vascular tissues, pointing to its neurovascular etiology.

Trigeminovascular system has been considered the source of nociceptive pain in migraine,<sup>5</sup> where first-order neurons in this system are activated, and their afferent fibers reach the meninges and their vessels, these last where a high density of C-fibers and A $\delta$ -fiber axons are found, explaining why when there is a mechanical or electrical stimulation of these vessels, can lead to a headache. First-order neuron axons can also reach the brain stem, sensitizing second-order neurons, including those in the spinal trigeminal nucleus, whose axons reach periorbital skin and pericranial muscles.<sup>5</sup> Afterwards, axonal projections coming from second-order neurons<sup>6</sup> reach the thalamus (cutaneous allodynia, headache exacerbation by light), brainstem (nausea, vomiting), hypothalamus (loss of appetite), upper cervical spinal cord (neck pain), and basal ganglia. This anatomy is very important, because when the trigeminovascular system is active, can lead to a parasympathetic outflow to the intracranial arteries,<sup>7</sup> releasing molecules including pituitary adenylate cyclase-activating peptide (PACAP), calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide, producing a major vasodilation of these arteries, but also, a generalized neurogenic inflammation state.6,7

Migraine without aura is clinically characterized by<sup>8</sup> at least 5 attacks of headache lasting between 4 and 72 h, which might be unilateral, with pulsating quality, moderate to severe in pain, and may cause avoidance of routine physical activity. Also, it can present with nausea and/or vomiting, photophobia, or phonophobia, and there are no other possible diagnoses (secondary cephalea has been ruled out). When migraine presents with aura,<sup>8</sup> it presents as classic (without aura headache-type) but, it includes fully reversible aura symptoms (visual, sensory, speech, language, motor, brainstem, or retinal) plus, at least one aura symptom which spreads gradually over 5 min, at least one aura symptom is unilateral, also, at least one aura symptom is positive; aura symptoms last between 5 and 60 min, and they are followed by headache.

Acute treatment for migraine attacks is based on the severity of the pain, associated symptoms, onset, and duration of the headache.<sup>9</sup> Non-steroidal anti-inflammatories (NSAIDs) are the first line for mild to moderate headache or in severe headache that have responded to this pharmacological group.<sup>7,10</sup> Acetylsalicylic acid, ibuprofen, and diclofenac have shown the best effectiveness among NSAID.<sup>7</sup> When there is no contraindication, triptans are the first line of management in severe attacks,<sup>9</sup> and there are seven oral triptans available for clinical use,<sup>7</sup> however, most of them have similar characteristics regarding efficacy, tolerability, and suitability.<sup>11</sup> Combination of these medications has shown a higher rate of relief than using either one as monotherapy.<sup>10</sup> But combinations are not limited to pain medications, management of migraines can include antiemetics, caffeine, and ergot derived.<sup>12</sup>

Preventive management is defined as therapy for reducing severity, duration, and frequency of migraine attacks,<sup>9</sup> in patients with >4 attacks per month,<sup>9,12</sup> but can be used in patients with poor response of medications during the acute attack, when the patient overuse analgesics and if the life quality is moderate/severely affected. Medications include non-selective beta blockers, antidepressants, calcium channel blockers, anticonvulsants, and some vitamins.<sup>9</sup> But these medications have poor adherence, mostly due to their adverse effects and poor tolerance. Life-style recommendations and behavioral therapy are also recommended in patients with chronic migraine,<sup>7,9,11,12</sup> but non-traditional (allopathic) therapies have risen as alternative management for this condition, including acupuncture. We aim this study to evaluate the impact and effectiveness of acupuncture in the management of migraine with or without aura.

#### Materials and methods

This scoping review followed the steps proposed by Arksey, O'Malley<sup>13</sup> and Levac,<sup>14</sup> answering the questions: Is there any impact of acupuncture in the severity, duration, and frequency of migraine? Is there evidence regarding the effectiveness of acupuncture in the management of acute migraine attacks? And, if there is an impact of acupuncture

in the life-quality in patients with migraine? Based on these three questions, a research protocol was developed for conducting this scoping review.

## Protocol

Before the beginning of this scoping review, there was a protocol developed based on the PRISMA-P guidelines for systematic reviews and scoping reviews<sup>15</sup> (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol).

## Inclusion and exclusion criteria

Inclusion criteria were: 1. Theoretical publications (narrative reviews, systematic reviews, meta-analysis) or clinical trials. 2. The objective of the publication is to evaluate or discuss the impact/use of acupuncture in the management of migraine (with or without aura) (either in acute attacks or as preventive therapy). 3. The clinical trial / publication shows results regarding the use of acupuncture in patients with migraine (either in acute attacks or as preventive therapy). 4. Languages considered in this publication are English, Spanish, and French. All the publications that did not meet the criteria were excluded. There was no date limit in this research, with the last update on May 27, 2021.

# Research strategy

Databases included were SCOPUS and Pubmed. Also, there were included registers from 18 databases from the International Clinical Trials Platform from the World Health Organization (WHO)<sup>16</sup>: Chinese Clinical Trial Registry, U.S. National Library of Medicine, German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), EU Clinical Trials Register (EU-CTR), Japan Primary Registries Network (JPRN), Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), ISRCTN, Peruvian Clinical Trial Registry (REPEC), Clinical Research Information Service (CRiS) - Republic of Korea, Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials RPCEC), The Netherlands National Trial Register (NTR), and Pan African Clinical Trial Registry (PACTR). Based on each data system, there were used keywords and boolean operators. The research algorithm is available on supplement 1.

### Selection of publications and data collection

Using Rayyan,<sup>17</sup> a free website for managing systematic reviews, authors review and choose all possible titles and abstracts. Then, they were into meetings discussing and solving discrepancies. After that, they remove duplicates and get full documents through the Universidad de la Sabana and Universidad Nacional library.

Next step was data extraction. There were tables created based on the variables which will answer research questions, one table was used for clinical trial entries and another for the other kind of publications. Data was selected, described, and analyzed based on the method recommended by Arsey and O'Malley,<sup>13</sup> making all the information extracted standard. The created formats were adjusted using 5% of the documents for assuring if the applied method was appropriate, then, the remaining information was extracted.

The information extracted from publications include authors, document-type (e.g., systematic review), objective, journal, country, and main findings. For clinical trials, information extracted included: ID code, recruitment state, country, sample size, intervention, control, primary outcome, starting/registered date, and completion date.

## Integration and presentation of results

The results of this scoping review are shown following the categories proposed by Grudniewicz et al.,<sup>18</sup> which include: a) a summary of the characteristics and distribution of the included publications, b) a summary of the results. As mentioned in the protocol, results will be presented using the PRISMA extension for scoping reviews (PRISMA-ScR).<sup>15</sup> A checklist was developed, which was completed, and is included in the supplement 2.

# Results

In this scoping review, a total of 84 documents were included (bibliography available in supplement 3) and 62 clinical trials (Fig. 1).

# **Clinical trials**

There are 62 clinical trials, including interventional parallel studies (n=52; 83.87%), interventional, single group assignment, non-blinded trials (n=6; 9.67%), case-controls study (n=1; 1.61%), prospective cohorts (n=2; 3.22%), and prospective observational study (n=1; 1.61%). These are mostly from China (n=34), followed by United States (n=5), Iran (n=4), Germany (n=3), Japan (n=3), Brazil (n=3), Australia (n = 2), Spain (n = 2), Taiwan (n = 2), Indonesia (n = 2) 1), France (n=1), and Czech Republic (n=1). The total population evaluated is 9079 patients. The main outcomes evaluated are changes in frequency, intensity, and number of headaches after treatment. Most of them are completed (n=38), 9 studies are recruiting, 13 of them are active but not recruiting, 1 of them (UMIN000028222) has no available information in the clinical trial databases and the NCT01481103 trial was terminated by the main investigator, it was reported due personal circumstances. The principal features of these studies are available in Table 1. The biggest study (ISRCTN18249834) evaluates the efficacy of verum acupuncture compared with sham acupuncture and standard medical management.<sup>19</sup> The primary outcome was the difference in migraine days in the period between 4 weeks before randomization and weeks 23-26 after randomization. Results shown a mean reduction of 2.3 days of headache in the verum acupuncture group (95% CI, 1.9–2.7), 1.5 days in the sham acupuncture group (95% CI, 1.1-2), and 2.1 days in the standard therapy group (95% CI, 1.5–2.7), but without statistical difference between all groups (p = < 0.01). There was also no difference between the three treatment groups regarding secondary outcomes (p = < 0.01). When compared between each other, there are no findings for

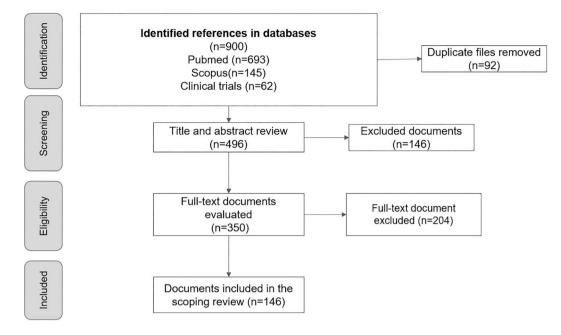


Fig. 1. PRISMA-R Chart (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol) implemented for this scoping review. Source: Authors.

suggesting physicians to choose one or another, however, if they are compared as in a non-inferiority trial, all treatments were effective improving in the number of migraine days, but with better results for verum acupuncture than sham acupuncture, mostly because sham acupoints were applied superficially on upper arms, thighs, and both scapulae, but they did not consider head or other specific acupoints for migraine. However, an interesting finding was that sham acupuncture was actually effective, showing that needles might have a biological effect similar to the verum acupuncture when it is applied to specific points.

Yang et al.<sup>20</sup> evaluated the impact of traditional acupuncture on migraine without aura. The primary outcomes of this trial included difference in the visual analogue scale (VAS) after the treatment and the brain glucose metabolism evaluated with a PET-CT scan, results were compared with patients subjected to electroacupuncture, and patients with no treatment. VAS pain intensity was reduced by traditional acupuncture (p=0.0005) and by electroacupuncture (p=0.008), but there was no significant reduction in pain intensity in patients with no treatment (p= 0.047). Regarding PET-scan results, when patients were subjected to traditional acupuncture, metabolism was increased when compared to patients with migraine but without treatment, in the middle temporal cortex, insula, middle frontal gyrus, precuneus, orbital frontal cortex, and middle cingulate cortex. It was also found that metabolism was decreased in parahippocampus, hippocampus, fusiform gyrus, postcentral gyrus, and cerebellum. These findings suggest that acupuncture can model the pain matrix within the brain and generate an important pain modulation through endogenous opioid modulation (orbital frontal cortex), and pain processing (hippocampus and insula), suggesting acupuncture can be an alternative treatment in patients with migraine without aura.

But trials were not only limited to evaluate its application in the outclinic patient, Cohen et al.<sup>21</sup> evaluated the impact of acupuncture in the emergency room, as pain management of ankle sprain, low back pain, and migraine. The evaluation compared acupuncture alone, acupuncture plus pharmacological management, or standard care, but they found migraine unlike the other two conditions, neither statistical analyses indicated equivalence, nor non-inferiority. All therapies showed a decrease in the pain scale score after the beginning of the treatment, with a mean decrease of 2.1 points in VAS scale, and after the first hour, a decrease achieved 6.4 units, but there was no statistical significance between any therapy (p=0.57). Also, it is good to point out that none of the therapies successfully afforded patients in the emergency department, because most of them after the first hour had a VAS > 4, and less than 40% had at least a 2-point VAS decrease, however, acupuncture alone was the only therapy that patients would repeat as management of any of these conditions, when compared with pharmacological management (47%-61% vs. 57%-52%). Acupuncture alone was also the therapy that actually needed more rescue dose (oral opioid offered in this study), but there cannot be established if acupuncture by itself failed as treatment or patients felt they had missed out on standard care, but regardless this situation, acupuncture can be a safe and useful alternative in the ER setting, in the multi-modal approach for pain management as a non-pharmacological therapy, but also, its implementation can increased the patient satisfaction when there are contraindications for certain drugs.

#### **Documents included**

A total of 84 documents were selected for this scoping review, including clinical trials (n=34; 40.47%), prospective

Table 1 C	Document	e publications included in the Objective		Journal	Country	Main findings /
AUTIOIS	Document	Objective	Tear	Journal	Country	Contributions
Ahn CB, et al.	Prospective cohort trial	Develop effective treatment using combined acupuncture (CA) - traditional acupuncture and ear acupuncture - and to set clinical protocols for future trials.	2011	Journal of Acupuncture and Meridian Studies	Korea	Traditional or combined acupuncture, was associated with a reduction in pain in headache, migraine, trigeminal neuralgia, and retroauricular pain in facial paralysis, but no significant differences between them.
Alecrim- Andrade J, et al.	Randomized sham-controlled trial	Evaluate semi-standardized acupuncture efficacy in migraine prophylaxis.	2006	Cephalalgia	Brazil	Acupuncture shows no difference from sham acupuncture in preventing migraine attacks. No statistically significant difference about headache severity, frequency, or duration of migraine attack, either regarding associated symptoms or rescue medication.
Alecrim- Andrade J, et al.	Prospective cohort trial	Assess the efficacy of acupuncture in migraine prophylaxis.	2008	The Clinical Journal of Pain	Spain	Real acupuncture group showed improvement with significant differences in the number of days with migraine and migraine attack frequency in the first and second months. In the last month of the treatment was presented a high improvement of the sham acupuncture group, these differences disappeared,
Allais G, et al.	Randomized controlled trial	Evaluate the effectiveness of acupuncture versus flunarizine in the prophylactic treatment of migraine without aura.	2002	Headache	Italy	The number of attacks after 2 months of therapy and analgesic consumption were significantly lower in the Acupuncture group, with pain intensity significantly reduced and less side effects, but at 6 months no such differences existed between the two treatment groups.
Allais G, et al.	Prospective cohort trial	Evaluate TENS, infrared laser therapy and acupuncture in the treatment of transformed migraine,	2003	Neurological Sciences	Italy	The headache days significantly decreased in the TENS and laser therapy groups in the first month, but this became significantly lower in the Acupuncture group after the second month.
Allais G, et al.	Prospective randomized cohort trial	Verify the therapeutic value of area M and to compare it with an area of the ear which probably does not have a therapeutic effect on migraine attacks.	2011	Neurological Sciences	Italy	This study suggests that the therapeutic specificity of auricular points exists and is linked to the somatotopic representation of our body on the ear.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Backer M, et al.	Prospective cohort trial	Evaluate the effect of repetitive somatosensory stimulation (acupuncture) on cerebrovascular response in migraineurs by functional transcranial Doppler.	2004	Headache	Germany	Data indicate that repetitive somatosensory stimulation (acupuncture) might positively influence the abnormal cerebrovascular response in migraineurs. In a subgroup of migraineurs, however, the dysfunction of the cerebrovascular system might deteriorate under the treatment.
Bäcker M. et al.	Prospective cohort trial	Test whether the clinical effects of acupuncture in migraine prophylaxis are mediated by changes of the autonomic regulation.	2008	The Clinical Journal of Pain	Germany	Patients had a significant improvement in attack frequency, days with moderate or severe headache, and pain intensity, Verum acupuncture and sham acupuncture might have a beneficial influence on the autonomic nervous system in migraineurs, however, the mode of acupuncture did not have an influence on the clinical outcome.
Cayir Y. et al.	Prospective cohort trial	Evaluate the effect of acupuncture on the serum matrix metalloproteinase-2 (MMP-2) level and activity in patients with migraine.	2014	Acupuncture in Medicine	Turkey	The mean VAS was 85.5± 16.6 and was significantly decreased to 39.8±20.6 after 10 sessions of acupuncture, also, was a significant increase in quality-of-life score after acupuncture treatment.
Ceccherelli F. et al.	Randomized, controlled, blind study	Compare the effectiveness of somatic and ear acupuncture for treatment of migraine without aura.	2012	Acupuncture & Electro- Therapeutics Research	Italy	At the end of therapy pain was significantly lower for both groups, but after six months residual pain was so different between somatic (16.8%) and ear (48.83%) acupuncture. A decrease of depression score was present in both groups.
Chen YY, et al.	Meta-analysis	Compare acupuncture with propranolol using indirect treatment comparison meta-analysis.	2020	Journal of Neurology	China	Acupuncture was significantly better than propranolol, in reducing migraine frequency, with fewer migraine episodes and seemed to be better than flunarizine, metoprolol, propranolol + flunarizine, topiramate, and usual care; indirectly acupuncture was better than metoprolol in reducing migraine days.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Cohen MM, et al.	Multicentre, randomised, equivalence and non-inferiority trial	Assess analgesia provided by acupuncture, alone or in combination with pharmacotherapy, to patients presenting to	2017	The Medical Journal of Australia	Australia	Acupuncture caused fewer adverse events than propranolol, but the difference did not reach statistical significance. The effectiveness of acupuncture alone was comparable with that of pharmacotherapy. It may be useful as an adjunct to
	emergency departments with acute low back pain, migraine, or ankle sprain.		pharmacotherapy or when pharmacotherapy is unsuitable, but any therapy provides optimal acute analgesia during the first hour.			
Diener HC, et al.	Multicentre randomised controlled clinical trial	Assess the efficacy of verum acupuncture compared with sham acupuncture and standard migraine prophylaxis with beta blockers, calcium- channel blockers, or antiepileptic drugs in the reduction of migraine days.	2008	The Lancet Neurology	Germany	The mean reduction of migraine days was statistically significant compared with baseline, but not across the treatment groups (sham acupuncture, verum acupuncture, or standard therapy).
Endres HG, et al.	Narrative Review	Look at current studies on acupuncture and migraine and discuss the results.	2007	Expert Review of Neurotherapeutics	Germany	A long-term pharmacological treatment for migraine prophylaxis is not superior to acupuncture treatment, the patients show a clinically relevant reduction in migraine symptoms compared with baseline, No significant difference was found between verum and sham acupuncture with respect to the reduction in the
Endres HG, et al.	Multicentre, sham- controlled, patient and observer- blinded, randomised trial	Investigate the effects on headache frequency of verum acupuncture vs. sham acupuncture, in patients with episodic or chronic TTH	2007	The Journal of Headache and Pain	Germany	number of migraine days. TTH improves after acupuncture treatment, 33% of verum patients and 27% of sham controls were classed as responders. Verum was superior to sham acupuncture for headache days and the International Headache Society response criterion.
Facco E, et al.	Prospective, randomized, controlled study	Check the effectiveness of a true acupuncture treatment in migraine without aura, comparing it to a standard mock acupuncture protocol, an accurate mock acupuncture healing ritual, and untreated controls.	2008	Headache	Italy	Data suggest that traditional acupuncture is an effective tool for migraine prophylaxis: the syndrome differentiation according to TCM seems to work, although we do not yet know whether all TCM syndromes are so relevant as to call for a specific acupoint selection.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Facco E, et al.	Prospective, controlled study	Compare the effectiveness of traditional acupuncture and valproic acid in migraine prophylaxis.	2013	Minerva Anestesiologica.	Italy	Data show a lower pain intensity and lower Rizatriptan intake at six- months follow-up with no adverse events in acupuncture patients compared to those treated with valproic acid.
Ferro EC, et al.	Randomized controlled trial	Investigate the efficacy and tolerability of acupuncture, Tanacetum or combined treatment on quality of life in women with chronic migraine.	2012	Acupuncture in Medicine	Brazil	Improvement of the quality of life and better analgesic effect of acupuncture combined with tanacetum treatment on migraine pain in women when compared with acupuncture or tanacetum alone.
Foroughipor M. et al.	Prospective randomised cohort trial	Assess the effects of adding acupuncture to conventional migraine prophylaxis.	2014	Acupuncture in Medicine	Iran	Was a reduction in the number of attacks by both true and sham acupuncture, but this reduction was significantly greater in the true acupuncture group. The efficacy of acupuncture treatment gradually decreased over time so that the difference between the numbers of attacks was minimal at the end of the fourth month.
Foster NE, et al.	Meta-Analysis	Analyzed the Acupuncture Trialists' Collaboration dataset to identify subgroups of chronic pain patients who might be responsive to acupuncture compared to control treatments.	2021	Acupuncture in Medicine	United States	They did not find evidence to support the notion that there are exceptional acupuncture responders. The challenge remains to identify features of chronic pain patients that can be used to distinguish those that have a good response to acupuncture treatment
Giovanardi CM. et al.	Systematic Review	Assess the efficacy and safety of acupuncture for the prophylaxis of episodic or chronic migraine in adult patients compared to pharmacological treatment.	2020	Frontiers in Neurology	Italy	-

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Gottschling S, et al.	Randomized Controlled Trial	Investigate whether laser acupuncture is efficacious in children with headache and if active laser treatment is superior to placebo laser treatment	2008	Pain	Germany	They conclude that laser acupuncture can provide a significant benefit for children with headache with active laser treatment being clearly more effective than placebo laser treatment.
Jiang Y. et al.	Systematic Review	Evaluate the efficacy and safety of acupuncture for the treatment of migraine, and to confirm the effect of acupuncture for improving anxiety.	2018	Frontiers in Pharmacology	China	VAS scores were lower with acupuncture than with medication at 1–3 months after treatment and lower compared with sham acupuncture at 1 month.
Li X. et al.	Systematic Review	Assess the clinical efficacy and safety of Electroacupuncture treatment for migraine as the basis for reliable clinical strategies for patients with migraine.	2019	The American Journal of Chinese Medicine	China	Electroacupuncture was superior to control treatment (Western medicine, sham-EA, blank control, acupuncture, and acupoint catgut embedding), with lower VAS score, frequency of headache attack, self-rating anxiety scale and self-rating depression score.
Li Y, et al.	Randomized controlled trial	Discuss the results of a multicenter randomized controlled trial of the efficacy of verum acupuncture in treating acute migraine attacks.	2009	Headache	China	Verum acupuncture is more effective than sham acupuncture in reducing the discomfort of acute migraine. Verum acupuncture is also clearly effective in relieving pain and preventing migraine relapse or aggravation. Support that there are specific physiological effects that distinguish genuine acupoints from non acupoints.
Li Y, et al.	Randomized controlled trial	Assess the efficacy of acupuncture at migraine- specific acupuncture points compared with other acupuncture points and sham acupuncture.	2012	Canadian Medical Association Journal	China	Patients in the acupuncture groups reported fewer days with a migraine compared with control. Was a significant, but not clinically relevant, benefit for almost all secondary outcomes (frequency of migraines, intensity of pain) in the three acupuncture groups, without relevant differences between the groups.
Li Z, et al.	Prospective cohort trial	Explore how an effective treatment (verum acupuncture) could modulate the amplitude of low-frequency fluctuations of Migraine without Aura patients.	2017	Neurolmage: Clinical	China	Verum acupuncture showed significant improvement in VAS score and headache frequency, Verum and sham acupuncture modulates amplitude of low-frequency fluctuations of trigeminocervical complex in patients with migraine.

Table 1 (cor	ntinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Li Z, et al.	Randomized controlled trial	Investigate the resting- state functional connectivity (rs-fc) of the right frontoparietal network (rFPN) between migraineurs and healthy controls (HCs) in order to determine how the rFPN rs- fc can be modulated by effective treatment.	2017	Cephalalgia	China	Results suggest that migraineurs are associated with abnormal rFPN rs-fc. An effective treatment, such as acupuncture, may relieve symptoms by strengthening the cognitive adaptation/coping process. Elucidation of the adaptation/coping mechanisms may open up a new window for migraine management.
Linde K, et al.	Randomized controlled trial	Investigate the effectiveness of acupuncture compared with sham acupuncture and with no acupuncture in patients with migraine.	2005	JAMA	Germany	The reduction of the mean days with moderate or severe headache was equal between acupuncture and sham acupuncture groups (- 2.2 days), with 51% and 53% responders respectively, the reduction of days with headache in the waiting group was -0.8 days, with 15% responders.
Linde K, et al.	Pooled analysis of randomized controlled trials	Investigate the influence of expectations on clinical outcome in trials of acupuncture in patients with migraine, tension-type headache, chronic low back pain, and osteoarthritis	2007	Pain	Germany	A significant association was shown between better improvement and higher outcome expectations. The odds ratio for response between patients considering acupuncture an effective or highly effective therapy and patients who were more sceptical was 1.67, for personal expectations and confidence after the third session, odds ratios were 2.03 and 2.35), respectively.
Linde K. et al.	Narrative Review	Investigate acupuncture effectiveness versus routine care or sham acupuncture, in reducing headache frequency in patients with migraine.	2009	Cochrane	Germany	Patients receiving acupuncture had higher response rates and fewer headaches, compared to routine care only, There was no statistically significant superiority to true acupuncture over sham acupuncture. Acupuncture had slightly better outcomes and fewer adverse effects than prophylactic drug treatment.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Linde K. et al.	Narrative Review	Investigate whether acupuncture is more effective than no prophylactic treatment/ routine care only; than 'sham' (placebo) acupuncture; and as effective as other interventions in reducing headache frequency in patients with episodic or chronic TTH	2009	Cochrane	Germany	They found statistically significant and clinically relevant short-term (up to 3 months) benefits of acupuncture over control for response, number of headache days and pain intensity.
Linde K. et al.	Narrative Review	Investigate whether acupuncture is more effective than routine care only; sham acupuncture; and as effective as prophylactic drugs treatment in reducing headache frequency in adults with episodic migraine.	2016	Cochrane	Germany	Acupuncture was associated with a moderate reduction of headache frequency over no acupuncture, a small but statistically significant frequency reduction over sham acupuncture and a reduced migraine frequency versus drug prophylaxis.
Linde M, et al.	Randomized placebo- controlled study	Examine the role of needling per se in acupuncture as prophylaxis for menstrual-related migraine	2005	Cephalalgia	Sweden	No significant differences were found between the verum and the placebo groups, either in the attack frequency or in the number of days per month with migraine, headache intensity or drug-use.
Liu J, et al.	Double-blinded, randomized, placebo- controlled trial	Investigate the brain structural and functional changes for migraine attacks, and if it could predict placebo hypoalgesia	2017	Human Brain Mapping	China	Individual differences for the brain structure in the pain modulatory system is related to how an individual facilitated or diminished hypoalgesia responses to placebo treatment in migraineurs.
Lo MY, et al.	Systematic review	Review the cerebral hemodynamics involved in acupuncture and migraine headache, elucidated by modern brain imaging techniques.	2013	Journal of Traditional and Complementary Medicine	Taiwan	Acupuncture may positively influence cerebral autoregulation during the interictal phase. Needling at angles connecting acupoints may be clinically superior to standard acupuncture.
Lo MY, et al.	Systematic review	Review the literature investigating the effect of acupuncture on muscular and/or cerebral microcirculation.	2015	Evidence-Based Complementary and Alternative Medicine	Taiwan	Acupuncture influences regional oxygen saturation in cerebral and muscular tissue. Acupuncture may modulate dysfunction in cerebral autoregulation.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Meissner K, et al.	Systematic Review	Investigate whether different types of placebo treatments are associated with different responses	2013	JAMA Internal Medicine	Germany	Sham acupuncture and sham surgery were associated with a more pronounced reduction of migraine frequency than oral pharmacological placebos
Melchart D, et al.	Narrative Review	Determine whether acupuncture is more effective than no treatment, 'sham' (placebo) acupuncture and as effective as other interventions used to treat idiopathic (primary) headaches.	2001	Cochrane	Germany	True acupuncture was reported to be significantly superior in migraine and tension-type headache patients.
Melchart D, et al.	Randomized controlled trial	Investigate whether acupuncture is superior to placebo and equivalent to sumatriptan for the early treatment of an acute migraine attack.	2003	Journal of Internal Medicine	Germany	Acupuncture and sumatriptan were more effective than a placebo injection in the early treatment of an acute migraine attack. Sumatriptan was more effective than acupuncture at relieving headache.
Nie L, et al.	Randomized controlled assessor-blind clinical trial	Explore the effectiveness of acupuncture combined with tui na therapy in patients with migraine.	2019	Complementary Medicine Research	China	The total effective rate of acupuncture with tui na treatment was 95.6%, acupuncture 88.9%, and 75.6% for control group (flunarizine hydrochloride, with a significant reduction in attack frequency, severity of pain, duration of migraine, and associated symptoms.
Ou MQ, et al.	Systematic review	Investigate the efficacy and safety of acupuncture for migraine, and transcranial doppler changes after acupuncture.	2020	Frontiers in Neurology	China	Acupuncture was more effective than sham acupuncture and medication groups, with greater improvement in VAS score and lower adverse reaction rate. About improvement of intracranial blood flow the results were heterogeneous and unreliable.
Park J,et al.	Narrative Review	Summarize information from the Society for Acupuncture Research with studies on low back pain, knee osteoarthritis, migraine, tension-type headache, neurological conditions, psychiatric disorders, and functional bowel disorders.	2008	The Journal of Alternative and Complementary Medicine	United States	Verum acupuncture was at least as effective as migraine prophylaxis with beta blocker, with less number of headache days (the differences between verum and sham acupuncture was not significant). Patients receiving acupuncture took less medication.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Streng A, et al.	Prospective randomized cohort trial	Investigate whether acupuncture is as effective and safe as metoprolol in the prophylactic treatment of migraine	2006	Headache	Germany	The reduction in the number of migraine days and the proportion of responders was better in the acupuncture group, with fewer adverse effects, but results were not significant.
Sun Y, et al.	Systematic Review	Evaluate the efficacy of acupuncture for treatment of chronic headache.	2008	Anesthesia & Analgesia	England	Needling acupuncture is superior to sham acupuncture and medication therapy in improving headache intensity, frequency, and response rate.
Tastan K, et al.	Prospective cohort trial	Investigate the effect of acupuncture, hypnotherapy, and pharmacotherapy in migraine treatments	2018	International Journal of Clinical and Experimental Hypnosis	Turkey	The percentage reduction in the MIDAS (disability) and VAS (pain) scores at the third month in the acupuncture and hypnotherapy groups was significantly higher than that of the pharmacotherapy group.
Trinh KV, et al.	Systematic review	Verify the efficacy of the conventional treatments used in Linde et al.'s 2016 comparison with acupuncture.	2019	Medical Acupuncture	Canada	Moderate evidence suggests that acupuncture is at least non-inferior to conventional treatments.
Vickers AJ, et al.	Randomized, controlled trial	Determine the effects of acupuncture on headache, health status, days off sick, and use of resources in patients with chronic headache.	2004	ВМЈ	United States	Acupuncture leads to persisting, clinically relevant benefits for patients with chronic headache, particularly migraine, with less headaches days per year, best headache score, and health status based on physical role functioning, energy, and health changes.
Wallasch TM, et al.	Randomized Controlled Trial	Evaluate the effect of acupuncture on cerebrovascular response in migraineurs by transcranial Doppler ultrasound.	2012	The Journal of Alternative and Complementary Medicine	Germany	Prophylactic treatment of migraineurs by standardized acupuncture might positively influence the dysfunction of the cerebrovascular response to autonomic stimuli, but not the cerebral vasotonus during rest.
Wang LP, et al.	Single-blinded, double dummy, randomized controlled trial	Evaluate the efficacy of acupuncture for migraine prophylaxis.	2011	Pain	China	The patients in the acupuncture group had better responder rates and fewer migraine days compared with the control group (flunarizine + sham acupuncture), No significant differences in reduction of pain intensity and improvement of the quality of life.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Wang LP, et al.	Multicenter Single Blinded, Randomized Controlled Trial	Investigate the efficacy of acupuncture for acute migraine attacks compared with sham acupuncture.	2012	Pain Medicine	China	Verum acupuncture group was superior to sham acupuncture group on relieving pain and reducing the usage of acute medication.
Witt CM, et al.	Meta-Analysis	Evaluate the impact of possible moderators on the effect of acupuncture treatment.	2019	The Clinical Journal of Pain	Switzerland	Patients reporting more severe pain at baseline experience more benefit from acupuncture compared to either sham- control or non-acupuncture control.
Xu J, et al.	Systematic review	Assess the therapeutic and preventive effect of acupuncture and its safety for migraine without aura.	2018	Journal of Integrative Medicine	China	Acupuncture had a significant advantage over medication in reducing frequency of migraine and better VAS score over medication and sham acupuncture, with less side effect reports.
Xu S, et al.	Multicenter, randomized clinical trial	Assess the efficacy of manual acupuncture as prophylactic treatment for patients with episodic migraine without aura.	2020	ВМЈ	China	Manual acupuncture resulted in a significantly greater reduction in the number of migraine days and in migraine attacks.
Yang CP, et al.	Randomized clinical trial	Investigate the efficacy and tolerability of acupuncture compared with topiramate treatment in chronic migraine prophylaxis.	2011	Cephalalgia	Taiwan	A significantly larger decrease in the mean monthly number of moderate/severe headache days was observed in the acupuncture group compared with the topiramate group, with greater percentage of responders, and greater improvement in health- related quality of life.
Yang CP, et al.	Randomized controlled trial	Identify predictive factors of outcome in patients with chronic migraine treated with acupuncture or topiramate	2013	The Clinical Journal of Pain	Taiwan	Patients with throbbing symptoms had better prognosis with acupuncture than those without throbbing. Higher scores in the general expectations for improvement predicted better responses in both treatment groups.
Yang J, et al.	Prospective randomized cohort trial	Investigate acupoint specificity.	2012	BMC Complementary and Alternative Medicine	China	Acupuncture stimulation of different points on similar body regions in migraine patients reduced pain and induced different levels of cerebral glucose metabolism in pain-related brain regions. These findings may support the functional specificity of migraine- treatment- related acupoint.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Yang M, et al.	Prospective randomized cohort trial	Investigated the brain metabolism changes of acupuncture analgesia induced by sub-specific acupoint and non-acupoint stimulation.	2014	Journal of Translational Medicine	China	Acupuncture stimulation at both sub-specific acupoint and non-acupoint yields ameliorating effect to migraine pain, but with evidently different patterns of brain glucose metabolism.
Yang M, et al.	Systematic review	Assess the efficacy of acupuncture on the frequency and pain intensity of menstrual migraine.	2020	BMJ Supportive & Palliative Care	China	Acupuncture was not superior to sham acupuncture in reducing monthly migraine frequency and duration, average headache intensity, and analgesic use
Yang Y, et al.	Systematic review	Identify the effectiveness of verum manual acupuncture compared with sham acupuncture for the treatment of migraine.	2016	Acupuncture in Medicine	China	Verum manual acupuncture was better than sham acupuncture with reduction in the recurrence rate, but no significant differences in headache intensity, frequency or duration, accompanying symptoms and use of medication.
Yu X, et al.	Prospective randomized and controlled cohort trial	Make comparisons between acupuncture and acupressure for preventing menstrual migraine.	2018	Journal of Acupuncture and Meridian Studies	Canada	Verum acupuncture and acupressure were more effective for reducing menstrual migraine days and peak pain during intervention, but not significant differences during the follow-up.
Zhang N , et al.	Systematic review	Compare the effectiveness of acupuncture treatment with conventional migraine preventative medications.	2020	Headache	United States	Acupuncture is just as effective and has fewer side effects than many of the standard pharmaceutical agents. But the heterogeneity of the studies limits the analysis.
Zhang Y , et al.	Prospective cohort trial	Investigate the modulatory effect of acupuncture on the resting-state functional connectivity of brain regions in migraine without aura patients.	2016	Chinese Journal of Integrative Medicine	China	Acupuncture treatment could increase the functional connectivity of brain regions in the intrinsic decreased brain networks in migraine without aura patients.
Zhao L, et al.	Multicentre randomized controlled trials	Investigated the adverse events associated with acupuncture, to assess the safety of acupuncture	2011	Trials	China	Acupuncture is a safe therapy with low risk of adverse events in clinical practice, including subcutaneous hematoma, bleeding, skin bruising and needle site pain. The risk factors for adverse events were related to the patients' gender and age and the local anatomical structure of the acupoints.

Table 1 (cont	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Zhao L, et al.	Randomized Controlled Trial	Compare the differences in brain activities evoked by active acupoints and inactive acupoints and to investigate the possible correlation between clinical variables and brain responses.	2014	PLOS ONE	China	The decrease in the VAS was related to the increased average regional homogeneity values in the anterior cingulate cortex and in the insula. Acupuncture might have the potential effect of regulating some disease- affected key regions and the pain circuitry for migraine.
Zhao L,et al.	Randomized Clinical Trial	Investigate the long-term effects of true acupuncture compared with sham acupuncture and being placed in a waiting-list control group for migraine prophylaxis.	2017	JAMA Internal Medicine	China	The mean change in frequency of migraine attacks decreased in the true acupuncture group by 3.2, in the sham acupuncture group by 2.1, and the waiting-list group by 1.4; true acupuncture may be associated with long-term reduction in migraine recurrence.
Zheng H, et al.	Secondary analysis of a Prospective cohort trial	Study whether a higher expectation of acupuncture is associated with better outcome improvements in patients with migraine.	2015	Acupuncture in Medicine	China	A high level of expectation after acupuncture treatment rather than at baseline was associated with better long-term outcome improvements in patients with migraine.
Uritz et al.	Narrative review	overview of the acupuncture as treatment of acute and chronic migraine	2020	Neurology and Therapy	United States	Acupuncture might be useful as treatment for migraine patients due to its measurable effects on both the duration and frequency of migraine attacks
Yin T, et al	Research article	Explore if the neuroimaging markers could predict the relief of the symptoms of patients with migraine MWoA following a 4-week acupuncture treatment.	2020	Frontiers in neurology	China	Demonstrated the feasibility and validity of applying machine learning technologies and individual cerebral spontaneous activity patterns to predict acupuncture treatment outcomes in patients with MWoA.
Luo W, et al	Research article	Investigate the modulation effects of continuous taVNS at acupoints on the functional connectivity of the bilateral amygdalae in MwoA.	2020	Neural Plasticity	China	Continuous taVNS at acupoints can modulate the functional connectivity between the bilateral amygdala and pain-related brain regions in MwoA, involving the limbic system, default mode network, and pain matrix, with obvious differences between the left amygdala and the right amygdala.

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
Li K, et al.	Research article	Examine the treatment- related effects of standard acupuncture treatment on the right frontoparietal network in migraine patients.	2015	The Journal of Headache and Pain	China	Their study provided new insights into the treatment- related neural responses in MWoA patients and suggested potential functional pathways for the evaluation of treatment in MWoA patients.
Biçer M, et al	Clinical trial	Investigate the efficacy of acupuncture in preventing migraine attacks.	2017	Turkish Journal of Physical Medicine and Rehabilitation	Turkey	Acupuncture may be an effective option in the migraine prophylaxis.
Zhen F, et al.	Clinical trial	Observe the clinical effects of electroacupuncture for	2014	Journal of Acupuncture and	China	Electroacupuncture is an effective therapy for
Quirico P, et al.	Clinical trial	migraine without aura. Evaluate the effects of the insertion of PC 6 Neiguan and LR 3 Taichong acupoints on the cerebral blood flow in the middle cerebral artery.	2014	Tuina Science Neurological Sciences	Italy	migraine without aura. Their data seem to suggest that these two acupoints have very different effects on cerebral blood flow. The insertion of PC 6 Neiguan probably triggers a vasodilation in the middle cerebral artery, while the pricking of LR 3 Taichong determines a rapid and marked vasoconstriction.
Mayrink WC, et al.	Research article	Assess the effectiveness of acupuncture as an auxiliary analgesic treatment for chronic headaches and their influence on the quality of life.	2018	Journal of Acupuncture and Meridian Studies	Brazil	The true acupuncture group showed greater effectiveness in reducing the intensity of pain, the number of crisis, the quantity of analgesics used, and improving the quality of life in patients with chronic headache, compared to sham
Park KH, et al.	Clinical trial	Study blood flow in extracranial arteries after performing Korean Hand Acupuncture therapy on migraine patients.	2009	MEDICAL ACUPUNCTURE	Korea	acupuncture. Acupuncture can modulate extracranial blood flow through collateral circulation, which may affect the intracranial blood flow in migraine patients.
Zou Y, et al.	Research article	To determine whether and how longitudinal acupuncture modulates the impaired default mode network in chronic migraine patients without aura.	2019	Hindawi Neural Plasticity	China	In patients with migraine there is an altered default mode network, and after acupuncture therapy there is regulation and normalization of this network that might be employed as a monitor of chronic migraine.
Ning Y, et al.	Prospective cohort trial	Study the modulatory effects of acupuncture on the amplitude of low	2017	International Journal of Clinical	China	Needling GB41 could change the amplitude of the intrinsic cortical

Table 1 (con	tinuación)					
Authors	Document	Objective	Year	Journal	Country	Main findings / Contributions
		frequency fluctuations in migraine without aura patients.		and Experimental Medicine		activity of the brain, related to the amplitude of low frequency fluctuations abnormalities in migraine without aura patients.
Allais G, et al.	Clinical trial	Identify the most important auricular zones for pain control by applying the needle contact test.	2010	Neurological Sciences	Italy	The most effective tender points in pain control were located on the antero internal part of the antitragus, the anterior part of the lobe and the upper auricular concha ipsilateral to the side of pain.
Gong J, et al.	Prospective cohort trial	Observe the clinical efficacy of electroacupuncture with different frequencies in treating migraine.	2021	Journal of Acupuncture and Tuina Science	China	Variable frequency compared with low frequency and high frequency electroacupuncture shows superior clinical efficacy in treating migraine.
Yang X-J, et al.	Prospective cohort trial	Investigate the use of imaging biomarkers to predict the outcome of acupuncture in patients with migraine without aura.	2020	Frontiers in Neurology	China	Pre-treatment brain structure could be a novel predictor of the outcome of acupuncture in the treatment of migraine without aura.
Ni X, et al.	Systematic review	To review the effectiveness of acupuncture in the treatment of migraine compared with other treatments	2020	Journal of Pain Research	China	There is a minimum effectiveness of acupuncture as management of migraine, however the evidence is still limited due to the low quality of the published studies.
Hesse J, et al.	Comparative, randomized trial	To compare the effects of dry needling of myofascial trigger points in the neck region to metoprolol in migraine prophylaxis.	1994	Journal of Internal Medicine	Denmark	Acupuncture can be considered as prophylaxis treatment in chronic migraine if metoprolol fails or has a contraindication for its use.
Gu T, et al.	Clinical trial	To investigate if there is a neurochemical response to acupuncture treatment		Journal of Pain Research	Canada	An increase in N- acetylaspartate/creatine was observed in bilateral thalamus in migraine without aura after the acupuncture treatment, which was correlated with the headache intensity score

Notes: TENS: Transcutaneous electrical nerve stimulation - TTH: Tension-type headache - TCM: Traditional Chinese Medicine - rFP: right frontoparietal network - rs-fc: resting-state functional connectivity - VAS: visual analogue scale - MIDAS: Migraine Disability Assessment - MWoA: Migraine without aura - taVNS: transcutaneous auricular vagus nerve stimulation.

cohort trials (n=18; 21.42%), systematic reviews (n=14; 16.66%), narrative reviews (n=7; 8.3%), research articles (n=5; 5.95%), meta-analysis (n=3; 3.57%), non-inferiority trial (n=1; 1.19%), pooled analysis of randomized controlled trial (n=1; 1.19%), and secondary analysis of a prospective cohort trial (n=1; 1.19%). Authors were mostly from China (n=32), followed by Germany (n=16), Italy (n=9), United States (n=5), Taiwan (n=4), Brazil (n=3), Turkey (n=3), Canada (n=3), Korea (n=2), Australia (n=1), Sweden (n=1), Iran (n=1), Spain (n=1), Denmark (n=1), Switzerland (n=1), and England (n=1). Main findings from these documents are available in Table 2.

Acupuncture has been evaluated in settings of acute migraine attacks or as prophylaxis. Wang et al.<sup>22</sup> evaluated the efficacy of traditional acupuncture for an acute migraine attack, comparing the implementation of verum versus sham acupuncture. In their study, the primary outcome was VAS reduction; where the verum acupuncture group reported a reduction of 2.4 points (baseline was  $5.7 \pm 1.4$ ) and the sham acupuncture group reduction was 0.9 points (baseline was 5.4  $\pm$  1.3), with an incidence rate of recurrence of 4–8% in both groups, with no statistical significance (p = 0.492). Li et al.<sup>23</sup> also evaluated the impact of acupuncture in an acute migraine attack, comparing verum acupuncture with two sham groups, measuring VAS difference within the first 4 h after therapy, reporting only difference at second (p=0.032) and fourth hour (p=0.007). The verum acupuncture group baseline of  $5 \pm 0.8$ ), sham acupuncture group 1 had a baseline of  $5 \pm 1.0$ ) and sham acupuncture group 2 had baseline of  $4 \pm$ 2.0). At fourth hour, verum acupuncture had a two points drop, sham acupuncture group 1 had a 1 point drop, and sham acupuncture group 2 had a 1.5 points drop, however there was not difference between verum and sham acupuncture at early stages of the treatment (p = 0.05), but, when second outcomes come up, verum acupuncture shows a greater effectiveness compared with sham acupuncture because at 24 hours, 40.7% of the patients had a complete resolution of pain, also 79.6% of people in this group did not experience recurrence or intensification of the pain, and over 30% rated verum acupuncture over 75% in the overall satisfaction (p < 0.05), and these results are greater when compared with sham acupuncture, because only 20.3% of the patients in this group had resolution at 24 hours, and 33% less patients had permanent effects between 24 and 48 hours when compared to verum acupuncture (48 vs. 37 patients), but after 24 hours there was no significant differences (p<0.05).

Regarding prophylaxis and prevention, Alecrim-Andrade et al.24 evaluated the impact of acupuncture in migraine prevention, where they compare real versus sham acupuncture with a 6-month post-treatment follow-up. The primary endpoint was the percentage of patients with >50% reduction in migraine attack frequency each month compared with the baseline period, with a highest difference during the second month. Results, when compared between baseline and second month of treatment, showed that responders rate (headaches attack drop >50%) was 45% versus 15% (p=0.021) comparing real against sham acupuncture, but the results were not only limited to it, hours per month of headache drop 55% versus 36% (p=0.002), and the percentage of patients with reduction of 40% or more in migraine attacks were 58% versus 10% (p=0.04), but results were similar between the third month of treatment and after six months post-treatment (p=0.021). Linde et al.25 also evaluate the impact of acupuncture preventing migraine attacks, with a primary outcome of evaluating the difference in headache days of moderate or severe intensity between the 4 weeks before and weeks 9-12 after randomization. Results presented showed that both real and sham acupuncture had a very similar baseline (5.2 vs. 5.0) of VAS, with 2.2 days of headache per week (difference between acupuncture vs sham acupuncture, 0.0 days; 95%, CI, -0.7 to 0.7 days, p=0.96). Responder patients (headaches intensity drop >50%) was 51% in patients with acupuncture versus 53% in patients subjected to sham acupuncture and 15% in controls (waiting list) (p=<0.001), but, when compared the secondary outcomes, verum acupuncture was superior to sham acupuncture and controls, and there was no statistical difference in the secondary outcomes between real versus sham acupuncture (most p values > 0.5, except for depression as symptom, p=0.18).

Prophylaxis was also compared with available FDAapproved drugs for chronic migraine. Chen et al.,<sup>26</sup> performed an indirect comparison with propranolol, based on 19 papers, finding that acupuncture was significantly better than propranolol diminishing migraine episodes (SMD - 0.74, 95% CI - 1.04 to - 0.44), frequency (SMD - 0.74, 95% CI -1.04 to - 0.44), with a safer profile than propranolol (RR 0.82, 95% CI 0.11 to 5.94), but it was not statistically significant. Giovanardi et al.,<sup>27</sup> evaluated a total population of 1484 patients from 9 different studies, finding that acupuncture reduces the number of migraine days per month (SMD -0.37, 95% CI -1.64 to -0.11), pain intensity (SMD -0.36, 95% CI: -0.60 to -0.13) dropout rate for any reason (RR 0.39; 95% CI 0.18 to 0.84) and due to an adverse event (RR 0.26, 95% CI 0.09 at 0.74), and has a better response rate (RR: 1.46, 95% CI 1.16-1.84), results in favor of acupuncture when compared with pharmacological prophylaxis of migraine.

### Discussion

According to NIH Consensus Development Conference on Acupuncture, it refers to acupuncture as<sup>28</sup> "insertion of needles through the skin into underlying tissues at different depths and at strategic points on the body to produce a desired therapeutic effect", and even it has been practiced over 3000 years, it was not only until 1979<sup>29</sup> when FDA give it the category as class III medical device and WHO included as treatment for at least 43 pathologies where it was considered as treatment in Western civilization.

Acupuncture application on migraine has been widely characterized based on the available literature. Migraine acupoints have been widely described,<sup>30</sup> including a standard set (GB12, GB20, GB21, and Bl10), with several variations depending on the headache location and accompanying symptoms. Sham acupuncture is used as compared to real acupuncture in several studies,<sup>29</sup> but, when it is applied, in some studies have been described a positive response to it, for example, Makary et al.<sup>31</sup> evaluated the impact of phantom acupuncture, a novel sham acupuncture technique that reproduces the acupuncture needling procedure without somatosensory tactile stimulation. Their work

Table 2 Characteristi	Characteristics of the clinical trials included in the scoping review.	rials includ	ed in the s	scoping review.				
Ð	Trial design	Country	Sample size	Intervention	Control	Primary outcome	Overall trial start/ registered date	Expected trial end date
ChiCTR2100044251 <sup>b</sup>	Interventional study, parallel, randomized non-blinded	China	60	Insertion point	Needle shallow stab non-point	- Change in the number of monthly headache onset	July 1, 2020	June 30, 2023
ChiCTR2100042963 <sup>b</sup>	Interventional study, parallel, randomized, double-blinded	China	156	Acupuncture treatment group of migraine senior physicians	Migraine acupuncture treatment group of junior physicians	- Days of headache - Number of headache attacks	March 14, 2021	November 30, 2023
ChiCTR2100042915 <sup>b</sup>	Interventional study, non- randomized, prospective cohort	China	108	Migraine acupuncture treatment group	Tension-type headache acupuncture treatment group	- Number of headache days - Number of headache attacks	February 22, 2021	November 30, 2023
ChiCTR2000034417 <sup>b</sup>	Interventional study, parallel, randomized, non-blinded	China	66	Acupuncture treatment	Flunarizine	<ul> <li>Frequency of migraine attacks</li> <li>Intensity of migraine</li> <li>fMRI</li> <li>Gut microbiota</li> </ul>	August 15, 2015	December 31, 2022
ChiCTR2000033995 <sup>b</sup>	Interventional study, parallel, randomized, non-blinded	China	278	True acupuncture group	- Sham acupuncture group - health control group	<ul> <li>Change in frequency of migraine attacks</li> <li>Brain functional magnetic resonance data</li> </ul>	July 1, 2020 July 1, 2022	July 1, 2022
ChiCTR2000033040 <sup>a</sup>	Interventional study, parallel, randomized, double-blinded	China	60	<ul> <li>- Arm 1: dry needling myofascial trigger points</li> <li>- Arm 2: dry needling myofascial trigger points and medication</li> </ul>	- Medication	- Headache	September 1, 2019	September 30, 2022
ChiCTR2000032854 <sup>b</sup>	Interventional study, parallel, randomized, non-blinded	China	212	acupuncture/Chinese medicine	Flunarizine	- Number of headaches per month	November 1, 2019	November 30, 2021
ChiCTR2000032795 <sup>b</sup>	Interventional study, factorial, non- randomized, non-blinded	China	30	Acupuncture	None	- Magnetic resonance spectrum data	January 1, 2020	December 31, 2021
ChiCTR2000032629 ª	Interventional study, parallel, randomized, non-blinded	China	60	Acupuncture Trigger Pain Points	Nerve block	<ul> <li>Headache score after treatment</li> <li>Overall efficacy</li> <li>Headache grading after treatment</li> </ul>	May 6, 2020	December 1, 2020

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	0	129	China 90 China 129

Table 2 (continuación)								
Ð	Trial design	Country	Sample size	Intervention	Control	Primary outcome	Overall trial start/ registered date	Expected trial end date
ChiCTR-INR-17010760 <sup>a</sup>	Interventional study, parallel, randomized, non-blinded	China	152	Arm 1: Auricular needling at TF4, AH6, C015 of C010, C012, C015 alternatively twice a week Arm 2: Auricular needling at A-shi points	<b>Arm 3:</b> Auricular needling at A-shi points twice a week. <b>Arm 4:</b> Sham-auricular needling at A-shi points twice a week	<ul> <li>Comparing intensity reduction among 4 groups from 9th to 12th week</li> <li>Comparing frequency reduction among 4 groups from 9th to 12th week</li> </ul>	April 1, 2016	December 31, 2017
ChiCTR-IOR-16008001 a	Prospective Observational Study, randomized,	China	40	cance a ween Balance Acupuncture Treatment	Acupuncture point	- fMRI	July 1, 2015	June 30, 2016
ChiCTR-TRC-11001813 °	Interventional study, parallel, randomized, non-blinded	China	30	Arm 1: specific stimulation of traditional acupoints Arm 2: non-specific stimulation	No treatment	- Metabolism of glucose in the brain - Visual Analogue Scale(VAS) variation	July 1, 2008	September 30, 2009
ChiCTR-IOR-15007495 <sup>b</sup>	Interventional study, parallel, randomized, non-blinded	China	60	Acupuncture (target disease migraine)	Arm 1: Acupuncture (target disease insomnia) Arm 2: Acupuncture (normal puncture in meridian points)	- VAS Scale - Headache Rating	March 31,2015	December 1, 2016
ChiCTR-TRC-14004842 °	Interventional study, parallel, randomized, non-blinded	China	210	Acupuncture	Arm 1: Sham Acupuncture Arm 2: No intervention	- Headaches days per month - Migraine frequence	October 1, 2014	October 1, 2017
ChiCTR-TRC-10000807 °	lel ed rs)	China	06	Acupuncture (shallow puncture in meridian points)	Arm 1: acupuncture (normal puncture in meridian points) Arm 2: acupuncture (normal puncture in	- Number of migraine outbreak days per month	October 1, 2010	December 31, 2012
ChiCTR-TRC-13003635 °	Interventional study, parallel, randomized, non-blinded	China	60	Acupuncture at active acupoints	Arm 1: acupuncture at inactive/placebo acupoints Arm 2: acupuncture at acupoints on other meridians	- Headache diar	June 18, 2012	June 18, 2014

Expected trial end date	December 31, 2010	February 28, 2023	December 2, 2014	January, 2011	September 30, 2018	June 29, 2010
Overall trial E start/ t registered c date	January 1, E 2008 3	February F 23, 2021 2	June 29, E 2010 2	July, 2008 J	March 1, S 2018 3	January 24, J 2008 2
Primary outcome	- Frequency of headache - Rate of no improvement	<ul> <li>Changes in pain intensity</li> <li>Changes in number of migraine attacks per 4 weeks</li> </ul>	- Improvement of headache frequency (within 4 weeks)	- Reduction of frequency and intensity of headaches	<ul> <li>Monthly attacks frequency</li> <li>Duration of attacks</li> <li>Pain severity</li> </ul>	- Number of days with migraine - Frequency of migraine attacks
Control	Anti-pain treatment by medicine	Sham acupuncture combined with flunarizine hydrochloride	non-acupoints	N/A	N/A	<b>Arm 1:</b> Acupoints of other meridians <b>Arm 2:</b> Non-acupoints
Intervention	Arm 1: Selection of puncture points will depends on the "Zheng". Electronic stimulating Arm 2: Superficial puncture without "De Qi" and no electronic stimulating Arm 3: Selection of acupuncture methods based on WHO recommendation. Electronic stimulating	Acupuncture combined with placebo	Arm 1: Specific points of Bladder meridian and Shanjiao meridian Arm 2: Non-specific points of Bladder meridian and Shanjiao meridian Arm 3: Specific points of Stomach meridian	Acupuncture	Acupuncture	Arm 1: specific acupoints of Shaoyang meridians Arm 2: Non-specific acupoints of Shaoyang meridians
Sample size	009	96	00	50	84	480
Country	China	China	China	United States	Turkey	China
Trial design	Interventional study, parallel, randomized, double blinded	Interventional study, parallel, randomized, double blinded	Interventional study, parallel, randomized, double blinded	Interventional, single group assignment, non-blinded	Interventional, single group assignment, non-blinded	Interventional study, parallel, randomized, triple blinded
Q	ChiCTR-TRC-07000024 °	NCT04766762 <sup>b</sup>	NCT01152632 °	NCT00714727 <sup>c</sup>	NCT04542811 <sup>c</sup>	NCT00599586 °

Table 2 (continuación)								
Ð	Trial design	Country	Sample size	Intervention	Control	Primary outcome	Overall trial start/ registered date	Expected trial end date
NCT01481103 <sup>e</sup>	Interventional, single group assignment, non-blinded	United States	6	Acupuncture	Over-the-counter medication	- Number and intensity of migraine headaches	July, 2011	April, 2013
NCT02765581 °	Interventional study, parallel, randomized, double blinded	China	150	Verum acupuncture	Arm 1: Sham acupuncture Arm 2: Standard treatment	<ul> <li>Change in the number of migraine days</li> <li>Change in the frequency of migraine attacks</li> </ul>	May 6, 2016	November 20, 2018
NCT02764996 °	Interventional, single group assignment, non-blinded	United States	26	Acupuncture	N/A	- Reduction of migraine headache pain	May 6, 2016	June 30, 2017
NCT04157192 <sup>b</sup>	Interventional study, parallel, randomized, double blinded	France	6	Acupuncture	Sham acupuncture	<ul> <li>Regional homogeneity map in Interventional group patients before and after the first real acupuncture session.</li> <li>Regional homogeneity map in Placebo group patients before and after the first real acupuncture session.</li> <li>Regional homogeneity map in Interventional group patients before and after the last real acupuncture session.</li> <li>Regional homogeneity map of Placebo group patients before and after the last placebo acupuncture session.</li> </ul>	November, 2019	June, 2021
NCT02681211 <sup>a</sup>	Interventional study, parallel, randomized,	United States	80	Acupuncture	Medication + fluids	- Change in baseline pain score by a numerical self-reported visual analog pain score (VAS)	February 2016	February 2022
NCT02580968 °	Interventional study, parallel, randomized, sinde-hinded	China	2	Electro-acupuncture	Flunarizine	- Migraine Disability Assessment March, 2015 Questionnaire (MIDAS)	March, 2015	December, 2017
NCT01687660 °	Interventional study, parallel, randomized, non-blinded	China	249	Acupuncture	Sham acupuncture	- Frequency of migraine attacks	September, 2012	September, 2014

<u>c</u>	<b>⊤</b>				+ v			
2	II lat design	country	size	III CEL A EI LI OI	CONTROL		טעפו מו נו ומו start/ registered date	Expected trial end date
NCT01096420 <sup>c</sup>	Interventional study, parallel, randomized, non-blinded	Taiwan	68	Acupuncture	Topiramate	<ul> <li>Mean monthly number of headache days with moderate or severe intensity</li> </ul>	August, 2008	August, 2010
NCT04509141 °	Interventional study, parallel, randomized, triple blinded	Indonesia	34	Acupuncture	Standard treatment	- Frequency, intensity and duration of headaches	July 5, 2019	August 30, 2019
NCT04636359 <sup>c</sup>	Interventional study, parallel, non- randomized, triple blinded	China	30	Acupuncture (Patients in this group have the history of migraine without aura more than 5 years)	Acupuncture (Patients in this group have the history of migraine without aura equal or less than 5 vears)	<ul> <li>Headache Intensity</li> <li>Headache Days</li> <li>Headache Frequency</li> <li>Dataset of functional magnetic resonance imaging on brain</li> </ul>	October 30, 2017	February 1, 2020
NCT03503734 °	Observational, prospective cohort	Germany	158	Integrated headache care	N/A	- Headache frequency	August 18, 2011	January 30, 2014
NCT03250754 <sup>c</sup>	Case-controls, retrospective	Spain	482	Electro-acupuncture	Pharmacological management	- Number of days with headache per month	March 20, 2017	April 30, 2018
DRKS00009803 °	Interventional study, parallel, randomized, non-blinded	Czech Republic	86	Acupuncture + standard management	Standard management	-Frequency, duration and intensity of migraines	October 20, 2015	December 15, 2017
IRCT201108097265N1 <sup>c</sup>	Interventional study, parallel, randomized, single blinded	Iran	100	True acupuncture	Sham acupuncture	- Number of monthly headache attacks	March 1, 2011	December 31, 2011
IRCT20200213046477N1 c	<u>_</u>	Iran	80	Auricular acupuncture	Sham acupuncture	- Headaches	December 8, 2018	October 23, 2019
IRCT20160813029327N17 c	<u>_</u>	Iran	100	Amitriptyline + propranolol + acupuncture	Amitriptyline + propranolol	<ul> <li>The average number of migraine attacks</li> <li>Intensity</li> <li>Duration of attacks</li> <li>Nausea and Vomiting frequency</li> </ul>	July 6, 2017	April 30, 2018
IRCT201404146186N3 <sup>c</sup>	Interventional study, parallel, randomized, non-blinded	Iran	100	Acupuncture	Botox injection		April 30, 2014	September 21, 2014

Table 2 (continuación)								
Q	Trial design	Country	Sample size	Intervention	Control	Primary outcome	Overall trial start/ registered date	Expected trial end date
UMIN000043893 <sup>a</sup>	Interventional study, parallel, randomized,	Japan	30	Acupuncture	Sham acupuncture	- Headache Impact Test	March 25, 2021	March 31, 2023
UMIN000028222 <sup>d</sup>	ingo burdou Interventional study, parallel, randomized,	Japan	40	Acupuncture	Healthy control	- Headache Impact Test	July 7, 2017	September 30, 2019
UMIN00005644 °	Interventional, Interventional, single group assignment,	Japan	10	Acupuncture	N/A	- Cerebral blood flow	July 22, 2011	March 31, 2014
ACTRN12609000989246 °		Australia	528	Acupuncture	Standard management	<ul> <li>Verbal Numerical Rating</li> <li>Scale (VNRS)</li> <li>Rescue therapy requirements</li> <li>in the ED</li> </ul>	November 17, 2009	December 10, 2015
ACTRN12605000314628 <sup>c</sup>		Australia	50	Acupuncture	Sham acupuncture	cy of migraine attacks 1 of migraine attacks 7 of migraine attacks	September 6, 2005	November 28, 2019
U1111-1190-6791 °	Interventional study, parallel, randomized,	Brazil	34	Acupuncture	Sham acupuncture	r Scale (VNS) stionnaire algesics used	January 1, 2016	September 19, 2017
ISRCTN13563102 °	Interventional study, parallel, randomized,	China	60	Verum acupuncture + placebo medicine	Sham acupuncture + topiramate	headache	July 21, 2017	August 31, 2020,
ISRCTN11800433 °	<u>ت</u>	China	100	Verum acupuncture	Sham acupuncture	- The number of migraine days during the 4th and 16th week after randomization.	February 1, 2017	February 1, 2019
ISRCTN 35577064 °	angle princed Interventional study, parallel, randomized, double blinded	Taiwan	60	Verum acupuncture	Arm 1: Sham acupuncture Arm 2: No acupuncture	<ul> <li>Headache frequency</li> <li>Headache duration</li> <li>Regional oxygenation of the cerebral cortex</li> <li>Regional oxygenation of the upper trapezius</li> </ul>	August 1, 2014	July 31, 2017

	Trial design	Country	Sample size	Intervention	Control	Primary outcome	Overall trial start/	Expected trial end
							registered date	date
ISRCTN98703707 °	Interventional study, parallel, randomized,	Spain	270	Verum acupuncture	Arm 1: Sham acupuncture Arm 2: Standard	<ul> <li>The difference in the number of Days before and after treatment</li> </ul>	February 1, 2008	December 31, 2010
ISRCTN49839714 °	Interventional study, parallel, randomized, single blinded	China	140	Verum acupuncture + placebo medicine	cture +	<ul> <li>Visual Analogue Scale (VAS) to assess the severity of migraine pain</li> <li>Short-From of McGill Pain Questionnaire (SF-MPQ)</li> <li>Change in frequency and duration of mioraine attacks</li> </ul>	June 1, 2007	June 30, 2009
ISRCTN93327878 °	Interventional study, parallel, randomized, non-blinded.	Brazil	37	Verum acupuncture	Sham acupuncture	- The percentage of patients with a reduction of $\geq$ 50% in migraine attack frequency and the total of the migraine days compared with the baseline	December 7, 2001	June 30, 2003
ISRCTN74335441 °	Interventional study, parallel, randomized, non-blinded	Brazil	67	Verum acupuncture	Sham acupuncture	- The percentage of patients with a reduction of $\geq$ 50% in migraine attack frequency and the total of the migraine days compared with the baseline	March 1, 2003	January 30, 2003
ISRCTN52683557 °	Interventional study, parallel, randomized, non-hinded	Germany	1295	Verum acupuncture	Arm 1: Sham acupuncture Arm 2: Standard management	sess the efficacy of dised acupuncture	April 25, 2002	June 15, 2006
ISRCTN18249834 °	Interventional study, parallel, randomized,	Germany 115	115	Acupuncture	Metoprolol (100/200mg) - Not provided	- Not provided	October 1, 2002	January 31, 2005
ISRCTN96537534 °	Interventional study, parallel, randomized, non-blinded	United States	401	Acupuncture	Standard management	- Pain, wellbeing, days off work and resource use	October 1, 1998	May 31, 2002

was applied in lower back pain, proving through fMRI that after application of this technique, there were activation of bilateral dorsolateral/ventrolateral prefrontal cortex, with pain reduction, moreover, these findings were also documented for migraine. Li et al.<sup>32</sup> evaluated how acupuncture (verum and sham) modify ascending and descending pathways in patients with migraine without aura, with findings including significant amplitude of low-frequency fluctuations (ALFF) increases at the left posterior insula and left putamen/caudate, and ALFF decreases in the bilateral middle occipital cortex/cuneus rostral ventromedial and bilateral medulla/ trigeminocervical complex, means impacting directly in the trigeminovascular nociceptive path, showing that acupuncture directly modifies the pain matrix in the brain, findings that might be confirmed and extended by ongoing clinical studies (ChiCTR2000034417, ChiCTR2000032795, ChiCTR1900025132, ChiCTR-IOR-16008001, NCT04157192).

Acupuncture evidence is growing regarding its implementation in several conditions like migraine, supported by different medical associations that consider this therapy useful as management in acute attacks and prophylaxis of chronic migraine,<sup>33</sup> but there are two important factors that might explain why acupuncture has been unexposed as plausible treatment, first, patient's belief and thoughts regarding acupuncture as management of chronic conditions. Based on Mao et al.<sup>34</sup> work, lack of communication between primary care physician and the patient, can lead to a non-use of this therapy, but also, as second reason, when the patient does not have proper address, it can lead to create unrealistic expectations of this treatment, prove of it was the systematic review made by Prady et al.,<sup>35</sup> where they evaluated 58 papers regarding the impact of expectations in the clinical outcome of acupuncture trials, finding some evidence that pre-randomization response expectancies can show an interaction with outcomes, and, that acupuncture has increased its application, especially in conditions difficult-to treat or medically with non-specific symptoms but with high-burden use of healthcare services, <sup>36</sup> then, a proper counseling should be addressed from primary and specialized care physicians, but also, from licensed acupuncturist, closing the gap between allopathic and traditional medicine.

Implementation of therapies in patients with chronic disease is usually expensive, especially with high-burden disease like migraine. Hansson-Hedblom et al.<sup>37</sup> evaluate the cost-effectiveness of managing migraine in Sweden and Norway, finding that in patients with few attacks per month (0-4), costs of management is about EUR 6221 (US 7588 dollars; reference value obtained on May 27, 20:49 GMT -5:00, ET from, [https://www.ecb.europa.eu/stats/ policy\_and\_exchange\_rates/euro\_reference\_exchange\_ rates/html/eurofxref-graph-usd.en.html]), and in patients with many attacks per month (25-31) costs can rise up to EUR 57832 (US 70543 dollars). But this situation was also evaluated in low- and middle-income countries by Linde et al.,<sup>38</sup> where they find the implementation of simple analgesics (e.g., acetylsalicylic acid) was the most cost-effective strategy for managing migraine attacks for less than US 100 dollars, but, if a triptan is needed, the incremental cost would be expected over US 10,000 dollars, and regarding prophylaxis, amitriptyline was the

most cost-effective medication. Liao et al.<sup>39</sup> evaluate acupuncture used long-term in patients with migraine and the medical expenditure, showing that acupuncture users had more outpatient visits than non-users, but they did have fewer medical expenditures (US 20,863.4  $\pm$  102,835.3 dollars versus 17,039.6  $\pm$  80,545.8) (p=0.01), showing that acupuncture can be a cost-effective complementary therapy in the management of migraine.

## Limitations

This scoping review has several limitations. First, there were only two databases included, Pubmed, that comprises over 32 million citations regarding biomedical literature and texts, and SCOPUS as is the largest abstract and citation database of peer-reviewed literature, both contributing to the quality of the publications chosen for this manuscript. Also, the languages evaluated were only English, Spanish, and French, which leads to show an important limitation based on the fact most of the available literature regarding acupuncture is written in Chinese, therefore, it was an impediment to acquire the available literature about this topic.

It should be mentioned that a scoping review only collects and analyzes information, but it does not evaluate the quality of the information evaluated, because it is based on a non-specific question for its design,<sup>13</sup> and this situation is ratified by PRISMA extension.<sup>15</sup>

# Conclusions

Despite of being a longstanding therapy, physiological bases of acupuncture are still poorly understood, however, based on the findings of this study, acupuncture is a safe, effective, and cost-effective therapy in the management of acute migraine attacks and also as prophylaxis for chronic migraine, but there are needed further studies to assess effectiveness with bigger populations in high-quality designed studies, as well as the results of ongoing clinical trials for increasing current knowledge and implementation of this therapy.

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# Conflict of interests

Authors declare to not have any conflict of interest.

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#### Appendix A. Supplementary data

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