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# Traditional and Evidence-Based Acupuncture in Headache Management: Theory, Mechanism, and Practice

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## Abstract and Introduction

### Abstract

Acupuncture, traditional Chinese needle therapy, has become widely used for the relief of headache. The history of the practice of acupuncture in the United States and the theoretical framework for acupuncture in Chinese medicine are reviewed. The basic scientific background and clinical application of acupuncture in the headache management are discussed.

### Introduction

About one million of American patients receive alternative medicine treatment, an estimated 10 millions visits each year.<sup>[1]</sup> In response to this growth, many US medical schools have created alternative medicine curricula and begun to form academic departments of alternative medicine.<sup>[2]</sup>

Acupuncture, probably the most celebrated example of alternative medicine, is an important therapy in China, Japan, and Korea. In recent years, with the growth of interest in alternative medicine, acupuncture has become more popular in the United States as a treatment option. Despite the fact that more scientific studies are needed to confirm the efficacy of acupuncture, the National Institutes of Health Consensus Development Panel (NIHCDP) issued a report in November 1997 stating "acupuncture may be useful as an adjunct treatment or an acceptable alternative or be included in a comprehensive management program."<sup>[3]</sup> This statement will be discussed below.

There are an estimated 10 000 acupuncturists in the United States, including approximately 3000 physician acupuncturists.<sup>[1]</sup> The practice of acupuncture is regulated by individual states,<sup>[2]</sup> whose medical boards disseminate clear guidelines for education and certification of physicians. For those licensed physicians who are interested in obtaining board certification as DABMA (Diplomate, American Board of Medical Acupuncture), the American Academy of Medical Acupuncture requires 200 hours of didactic and clinical training as a prerequisite for taking the board exam. Both passing the board exam and clinical experience of at least 500 medical acupuncture treatments are required for the application of diplomat status in the American Board of Medical Acupuncture.<sup>[4]</sup> Nonphysicians can be trained in acupuncture in 16 schools accredited by the US Government to give 4-year courses in acupuncture or oriental medicine.<sup>[2]</sup>

To western thinking, it is difficult to understand how acupuncture relieves headache by placing needles in the scalp and neck, or, by treating points in the hands and feet. This essay briefly reviews the historical and theoretical framework for acupuncture, the scientific evidence for its mechanism, efficacy in headache relief, safety profile, and potential difficulty in the clinical acupuncture research.

## History

Acupuncture is thought to have existed in China in one form or another since at least the Xia Dynasty (2000 to 1500 BC).<sup>[5]</sup> It was first recorded in 1800 BC in *The Yellow Emperor's Classic of Internal Medicine*.<sup>[6]</sup> Acupuncture was first brought to Europe in the 1700s and was introduced to the United States during the 19th to 20th centuries. Sir William Osler recommended acupuncture for the treatment of acute lumbago in his classic medical textbook.<sup>[7]</sup> In the 1950s China reported the use of electroacupuncture (EA) to obtain surgical analgesia.<sup>[1]</sup> In 1972, the National Institutes of Health gave its first grant to study acupuncture.<sup>[8]</sup> In 1973, an NIH acupuncture conference in Bethesda, Maryland concluded that "Acupuncture holds some promise as an anesthetic for certain surgical operations and for the treatment of some acute and chronic painful conditions."<sup>[9]</sup> However, two recent events have brought special attention to acupuncture for medical use. In 1996, the United States Food and Drug Administration changed the classification of acupuncture needles from Class III (experimental) medical devices to Class II (nonexperimental but regulated) medical devices.<sup>[10]</sup> Being Class III hindered standard use of acupuncture, as acupuncture could only be performed in approved research settings (eg, hospital laboratories).

In November 1997, the National Institute of Health (NIH) established a consensus development panel to evaluate the efficacy of acupuncture for treatment of different disorders.<sup>[3]</sup> A bibliography of 2302 references was provided to the panel and a conference audience of 1200. Twenty-five experts from different specialties presented data with relevant citations to the panel and the audiences. While many studies have demonstrated the potential of acupuncture, few of the studies meet the high quality of contemporary research standards. The review panel found equivocal results in different studies, poor design, small sample size, and the inadequate selection of placebo controls. Because many of the studies used nonneedling controls, it is difficult to interpret whether the outcome reflects true acupuncture efficacy or just placebo needling effect. Thereafter, NIHCDP evaluated the efficacy of acupuncture based on the "needling" effect reported in the literature and cautiously concluded that acupuncture *may be* efficacious in treating the adult postoperative and chemotherapy nausea and

vomiting, postoperative dental pain; useful as an adjunct treatment or an alternative in treating addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma; and that it be included in a comprehensive management program. In order to continue to examine the potential of acupuncture as a useful therapeutic option for various conditions, the NIHCDP recommended further high-quality controlled trials. More details about acupuncture research will be discussed below.

## Theory of Acupuncture in Traditional Chinese Medicine

From the Chinese perspective, acupuncture is necessarily embedded in a complex theoretical framework that provides conceptual and therapeutic directions. The theories of Yin and Yang, five elements (the evolutionary phases of fire, earth, metal, wood, and water), Qi (vital energy) and blood, meridians (acupuncture channels) and acupoints, provide the most important guidance for acupuncture treatment. These theories will be described very briefly below, interested readers may obtain detail explanation from the relevant textbooks.<sup>[5,11,12]</sup>

Firstly, Yin and Yang theory is among the most important principles underlying the practice of all the Chinese medicine. The concept of Yin and Yang is the generalization of the two opposite aspects in related objects and phenomena in the natural world. The Chinese believe that all the objects in the universe include the two opposite aspects of Yin and Yang. Some Yin-Yang examples include tranquility and motion, lower and upper body, parasympathetic and sympathetic system, meridians correlated with designated Yin (Zang) and Yang (Fu) organs (described below).<sup>[11]</sup> According to the concepts of the Chinese Medicine, disease and pain are the result of imbalance of the Yin and Yang, and acupuncture treatment aims to restore that balance.<sup>[11,12]</sup> Secondly, Qi and blood is another pair of important concepts in Chinese Medicine. The ancient Chinese believed that Qi is the vital energy or life force, and all that matters in the universe appears by the movements and mutations of Qi.<sup>[11]</sup> According to traditional tenets and beliefs, Qi circulates inside the meridians and supports every life process and every organic function. Qi and blood circulate and function together; that Qi is the major force driving the blood circulating in the vessels.<sup>[11,12]</sup> If Qi flows, the blood will move; if Qi stops, the blood will stop. Pain is the result of stasis or blockade of the meridian Qi flow and the subsequent blood stagnation. Thirdly, the internal organs, in Chinese medicine, are divided into two categories: Zang and Fu. Zang organs include heart, liver, spleen, lung, and kidney. Zang organs function to transform and store the essential Qi. Fu organs include gallbladder, stomach, large intestinal, small intestinal, bladder, and triple energizer. Their major function is to digest the food and excrete the waste. As in other fields of medicine, the diagnosis of Yin and Yang conditions of Zang-Fu organs can be accomplished by a detailed history inquiry, physical exam including pulse palpation and tongue inspection. Fourthly, concepts of Jing and Luo are important for acupuncture practice. The Jing-Luo meridian network consists of major meridians (Jin channels) and minor meridians (Luo collaterals). Jing-Luo meridians are distributed throughout the body and inside the meridians Qi flows continuously. There are 14 major meridians, including 12 "regular" and 2 "curious" meridians in the body.<sup>[13,14]</sup> They are named according to their distributed organs: lung, pericardium, heart, large intestine, triple energizer, small intestine, stomach, gallbladder, bladder, spleen, liver, and kidney. The abbreviation and alphabetic code endorsed by the World Health Organization (WHO) for these meridians are LU, PC, HT, LI, TE, SI, ST, GB, BL, SP, LR, and KI, respectively.<sup>[15]</sup> The two major curious meridians, include the conception vessel (Renmai, CV) and governor vessel (Dumai, GV),

locating at the midline of the head and trunk in the front and back, respectively. Acupuncture points are the sites through which the Qi of the organs is transported to the body surface via the above described meridians. The acupuncture points are divided into three categories: acupoints of 14 regular meridians, extraordinary points, and Ashi points. (1) Acupoints of 14 regular meridians are the major components of the acupoint system. (2) The extraordinary points locate in parts of the meridian network other than the 14 regular meridians. They are an important complement to the regular acupoint system and contribute to pain management. (3) Ashi points are also called tender points. They do not have specific names and defined locations, and they are highly important in the diagnosis and treatment of headache and pain. Lastly, the theory of five elements holds that all the objects and phenomenon in the universe are formed or derived from wood, fire, earth, metal, and water, each of which is designated specific characteristics. For example, wood represents objects or phenomenon with bending and straightening nature.<sup>[5,11,16]</sup> There exist creative and controlling interactions among these five elements and a paradigm including these five elements represents a model of acupuncture widely used in the Western countries, including the United States.<sup>[5,16,17]</sup> The treatment examples of this paradigm are described in reference books and are beyond the scope of this article.<sup>[16,17]</sup>

## Scientific Basis

Despite some preliminary experimental evidence supporting acupuncture's analgesic effect on the trigeminocervical complex either directly or indirectly, the exact mechanism remains unclear.

## Histological and Physiological Characteristics of Acupoints

One of the most controversial issues in the acupuncture treatment is whether needling the specific acupoints achieves better therapeutic effect than needling any point (ie, a point not recognized as an acupoint).<sup>[3]</sup> Histology and anatomy of acupoints have been studied.<sup>[18,19]</sup> They are in the vicinity of the small or large peripheral nerves and their bifurcations, neuromuscular attachments, blood vessels, ligaments, and suture lines of the skull.<sup>[18,19]</sup> Dung further found that all the acupoints in the face and forehead region are located along terminal or cutaneous branches of the trigeminal nerve and between muscular branches of the facial nerve.<sup>[20]</sup> Langevin and colleagues recently found an 80% correspondence between the sites of acupoints and the location of intermuscular or intramuscular connective tissue planes in postmortem tissue sections.<sup>[21]</sup> They also found that needling the true acupoints would penetrate different tissue structures compared to the nonacupoints. Histologically, needling true acupoints will penetrate first dermis and subcutaneous tissue, then deeper fascia or interstitial connective tissue. In contrast, needling the nonacupoints will penetrate the dermis, subcutaneous tissue, and reach the muscle and bone, less likely passing through or inserting into the deep fascia layer. Passing through the deep fascia connective tissue layer may provide an effect on the tissue known as "winding around the needle." It is not known exactly how this phenomenon affects the acupuncture treatment outcome. Experienced acupuncturists often find that manually rotating the needle will generate a local resistance around the needle that can be easily felt.<sup>[21]</sup> Researchers have found that this resistance is at least partially due to the traction on surrounding tissues.<sup>[22]</sup> The winding phenomenon is visible on ultrasonic imaging and results in the "grasp force" that prevents the needle from being pulled out.<sup>[21]</sup> Using the

computer-controlled needling instrument, a quantitative study found that the pull-out force in the acupoints is 18% significantly greater than at nonacupoints 2 cm away.<sup>[23]</sup> More traction or resistance occurs in the subcutaneous tissue and deep fascia of acupoints than at the nonacupoints (subcutaneous tissue only).<sup>[21]</sup> The winding phenomenon between the needle rotation and tissue whorl may lead to development of sensory signals via mechanotransduction.<sup>[24]</sup> This serves as one of the hypotheses explaining the distinction between true acupuncture versus placebo needling.<sup>[21]</sup> It is postulated that mechanical signals arising from acupoint stimulation can induce an effect including gene expression, protein synthesis, bio-physiological change, and extracellular matrix modification. The lasting modification of extracellular matrix surrounding the needle may in turn influence the other structures sharing this connective tissue matrix, such as sensory afferents, fibroblasts, immune, and vascular cells.<sup>[21]</sup> Therefore, needling the acupoints (vs. nonacupoints) will more likely create mechanical signals and subsequent bio-physiological effect. Several studies were done to observe the difference of physical property between acupoints and nonacupoints.<sup>[25-27]</sup> In Johansson's study, acupoints were first marked on the skin and the control points were then marked 3 mm away of each of them. The temperature and electrical resistance for each point were measured and analyzed statistically. The acupoints had significantly higher local skin temperature and lower skin electrical resistance, compared to control points. A later study by Hyvarinen indicated that the diameter of the low-resistance skin points ranged from 1.0 to 2.0 mm, and the distribution of these points resembled that of the classical acupoints.<sup>[27]</sup> Increased skin conductivity was also reported in the acupoints in rats and men, compared to the nonacupoints.<sup>[26]</sup> It is still unclear what contributes to the difference of skin electrical properties. Based on the distinction of skin electrical resistance and conductivity, diagnostic and therapeutic probes have been developed. Such probes can help the acupuncturists or researchers to locate the acupoints by detecting the fall of cutaneous electrical resistance of the patients,<sup>[28]</sup> and even be used for treatment of those points. Stimulation to the classical acupoints might achieve stronger analgesic effect, compared to the nonacupoints.<sup>[29]</sup>

### **Inhibitory Effect of Acupuncture on the Trigeminal Nucleus Caudalis and the Dorsal Horn**

The trigeminal nucleus caudalis (TNC) is the site of synaptic interaction between the first- and second-order nociceptive neurons. The TNC receives the trigeminal afferent pain signals from the cranial vessels and dura mater.<sup>[30]</sup> C-fos expression, a measurement of neuronal activity in the TNC, can be increased by stimulation of the superior sagittal sinus or by administration of substances (ie, nitric oxide agonist glyceryl trinitrate, 5-HT<sub>2B</sub> agonist m-chlorophenylpiperazine) known to induce the migraine.<sup>[31-33]</sup> Drugs known to abort the migraine, such as sumatriptan and valproate, reduce c-fos expression in the TNC.<sup>[31,34,35]</sup> Some experimental studies have demonstrated the suppressive effect of acupuncture on the TNC, as measured by c-fos immunoreactivity. Using animal models, EA to the acupoint Neiting (ST 44) was found to suppress the increased c-fos protein expression evoked by the tooth pulp stimulation (TPS)<sup>[36]</sup>; EA also suppressed the jaw opening reflex response to TPS or direct stimulation of the TNC in rat,<sup>[37,38]</sup> and the suppressive effect could be aborted by transection of the spinal trigeminal nucleus at the level of the obex.<sup>[38]</sup> Furthermore, EA also inhibited the evoked potential in TNC following the TPS.<sup>[39-41]</sup> The inhibitory effect of acupuncture on the TNC may be at least partially mediated by the suppression of substance P (SP) release locally. In the study from Takagi and Yonehara,<sup>[42]</sup> the potential in TNC evoked by TPS was coupled with the

increased release of local SP. EA suppressed both the evoked potential and release of SP in TNC, and this inhibitory effect was significantly antagonized by the pretreatment of naloxone or methysergide. This suggests that EA's effect on the TNC, including the release of SP, may involve the modulation from serotonergic and opioidergic systems. The TNC projects the trigeminal signal to various part of the rostral brain structures, including rostral trigeminal nucleus, nucleus solitary tract, reticular formation, thalamus, hypothalamus, ipsilateral cerebellum, limbic system, cingular cortex, insular cortex, and auditory/visual association area.<sup>[43]</sup> In turn, it receives the central inhibitory modulation from many structures including the rostral trigeminal nucleus, nucleus raphe magnus (NRM), dorsal raphe nucleus, periaqueductal gray area (PAG), rostral ventromedial medulla (RVM), locus ceruleus, parabrachial area, the insular cortex, hypothalamus, and somatosensory cortex.<sup>[43-45]</sup> There is experimental evidence demonstrating that acupuncture may be able to activate some of these TNC inhibitory structures. EA to the acupoint Quanliao (SI18) increased the c-fos protein expression in dorsal raphe nucleus, the locus ceruleus, the hypothalamus, the thalamus, the RVM in rat<sup>[46]</sup>; EA to the acupoint ST44 not only suppressed the increased c-fos protein expression in the TNC response to TPS, but also activated the c-fos protein expression in the PAG.<sup>[36]</sup> Using the electrophysiological technique, EA to the acupoint Zusanli (ST36) was found to increase the firing of the "excitatory" neurons in the NRM which, in turn, exerted the descending inhibition of the nociceptive response to noxious stimulation of the tail skin in the rat.<sup>[47]</sup> These neurons are likely serotonergic in nature.<sup>[47,48]</sup> In addition, the acupuncture's effect on the TNC may be influenced by the secondary somatosensory cortex. In the study by Reshetniak et al<sup>[49]</sup> the evoked potential of TNC induced by the TPS was inhibited by EA, and this inhibitory effect was decreased after the functional inactivation of the secondary somatosensory cortex.

### **Central Modulation of Acupuncture on the Spinal Dorsal Horn Neuron**

Stimulation of the superior sagittal sinus in the cat and monkey increases the c-fos activity in TNC and dorsal horns (DHs) at C<sub>1</sub> and C<sub>2</sub> levels.<sup>[32,50]</sup> The C<sub>1</sub> and C<sub>2</sub> cervical DH are considered to be the caudal functional extension of the TNC, and implicated in the migraine pathophysiology.<sup>[51]</sup> Most studies of acupuncture's effect on the spinal DH are nonspecific and often focus on the entire spinal cord. While the specific effect on the upper cervical neurons is still unknown, a review of its effect on DH neurons may give us a hint to help to understand the potential mechanism. Data from animal studies suggest that acupuncture may directly suppress nociceptive response of the spinal DH neurons. In the anesthetized dog model, EA increased the level of immunoreactive met-enkephalin in the cervical spinal cord and medulla.<sup>[52]</sup> The enhanced immunoreactivity of enkephalin in the spinal cord was correlated with increased pain threshold.<sup>[53]</sup> In addition, the expression of proenkephalin (precursor of enkephalin) mRNA in the spinal cord was also enhanced, suggesting increased biosynthesis of this precursor in the spinal cord.<sup>[54]</sup> Lee and colleague demonstrated that the increased c-fos expression in the spinal DH induced by noxious stimulation was inhibited by the EA, and this effect, in turn, could be reversed by naloxone.<sup>[55]</sup> In addition, acupuncture may be able to influence the DH cells indirectly by several mechanisms. Firstly, some studies have demonstrated that acupuncture may presynaptically inhibit the afferent pain transmission in the DH.<sup>[56-61]</sup> This may be mediated through a gate control mechanism via stimulation of A-beta fibers.<sup>[61]</sup> This inhibition associates with the increased release of enkephalin from the enkephalinergic interneurons in the

spinal cord during the acupuncture.<sup>[52]</sup> The enkephalin binds to opiate receptors at the endings of nociceptive primary afferents, suppresses the release of SP from these terminals, and results in a block of pain transmission.<sup>[62]</sup> Secondly, acupuncture may activate rostral brain structures that send descending inhibition to the DH neurons.<sup>[47,54,63-66]</sup> Neurons in the NRM project descending serotonergic inhibitory pathway to the DH cells in the substantia gelatinosa.<sup>[47,48]</sup> The NRM receives input from the PAG which is modulated by the hypothalamus and amygdala.<sup>[48]</sup> EA has been found to increase the mu binding sites in PAG, NRM, hypothalamus, and amygdala,<sup>[67]</sup> stimulating the release of beta-endorphin in the CSF and plasma.<sup>[66]</sup> Destruction or removal of the major sources of beta-endorphin—the hypothalamus and the pituitary—abolishes the analgesia resulting from EA,<sup>[64,68]</sup> suggesting that the analgesia of EA is in part mediated by the hypothalamus-pituitary-PAG-NRM descending inhibitory system. This pathway is also implicated in the central inhibition of the trigeminal nociception and may play a role in the migraine pathogenesis.<sup>[43]</sup> Besides the possible activation of NRM serotonergic descending inhibition to the spinal DH neurons, acupuncture may also activate structures that send the descending noradrenergic inhibitory pathway to the spinal DH neurons. Noradrenergic neurons in the reticularis paragigantocellularis lateralis (RPGL) in the medulla project a descending noradrenergic inhibitory pathway to the spinal cord.<sup>[65]</sup> Stimulation of RPGL in rat by EA increases the pain threshold, implicating the activation this antinociceptive system.<sup>[65]</sup> The major source of norepinephrine, the pontine locus ceruleus is activated by EA, with resultant increased c-fos expression in this location.<sup>[45]</sup>

## Peripheral Modulation of Acupuncture

Some cervical acupoints are very important and are frequently included in the treatment formula of both research studies and clinical treatment of migraine, tension-type headache, and cluster headache.<sup>[29,69-71]</sup> Needling these points likely alters the function of upper cervical neurons. For example, acupoints Fengchi (GB20) and Tianzhu (BL10) have long been documented in acupuncture textbooks<sup>[12,16]</sup> for headache treatment and are frequently mentioned in acupuncture studies of different kinds of treatments of headache.<sup>[29,70,71]</sup> Anatomically, needling these two acupoints will pass through the local skin and muscles innervated by C2-5,<sup>[72]</sup> effecting nociceptive input in the corresponding myotomes and dermatomes.

## Inhibitory Effect of Acupuncture on the Pain Processing in the Headache Patients

Several studies have demonstrated that acupuncture stimulates the change in some pain modulating substances in the headache patients. Nappi et al observed the temporarily but significantly higher increase in plasma opioid levels in the chronic post-traumatic headache patients after 5 minutes of acupuncture stimulation.<sup>[73]</sup> Another placebo-controlled study on 22 pediatric patients with migraine demonstrated that true acupuncture stimulated increased activity of opioidergic system including the increased release of beta-endorphin in the plasma. This was coupled with clinical improvement.<sup>[74]</sup> Low CSF met-enkephalin levels in cluster headache were elevated by acupuncture.<sup>[75]</sup> However, the relationship between CSF met-enkephalin and cluster headache is still unknown. Serum magnesium levels were also increased with acupuncture treatment of migraine, coupled with the clinical improvement.<sup>[76]</sup> Intracellular magnesium is considered an antagonist of NMDA (*N*-Methyl-D-

aspartate)-receptor<sup>[77]</sup> and this receptor is linked to the development of central sensitization of second-order neurons.<sup>[43]</sup> Ionized magnesium deficiency has been implicated in the pathogenesis of migraine and tension-type headache.<sup>[78-80]</sup>

In summary, acupuncture (especially EA) has demonstrated the potential of direct or indirect inhibition of TNC and DH neurons. This effect may be modulated by several pain neurotransmitters and peptides.

## Clinical Practice

Compared to studies in pain management, fewer studies are available investigating the efficacy of acupuncture in the treatment of headache disorders. Interpreting the efficacy of acupuncture in headache management is likewise difficult, due to difficulties in study design. Despite the absence of evidence-based medicine supported proof of efficacy of acupuncture in headache management, accumulated literature seems to suggest acupuncture as a potentially useful option for the treatment of migraine and tension-type headache. Even less scientific evidence evaluating acupuncture's role in the management of other types of headache exists. A systematic review by the Cochrane Collaborative assessed the efficacy of acupuncture in treatment of migraine, tension-type, and other types of headaches.<sup>[81]</sup> Twenty-six trials including 1151 patients were reviewed. Majority of the trials were found to have some methodological and/or reporting shortcomings and too small sample size. The Cochrane review concluded that straightforward recommendations for widely use of acupuncture in the clinical practice could not be made at present, but some forms of acupuncture seemed to be beneficial and those patients who wanted to try acupuncture should not be discouraged.

## Treatment Principle

Utilizing the principles of the Chinese medicine mentioned above, acupuncture aims to restore the balance of Yin and Yang, clean the blockade of meridians, and resume the Qi flow. Ultimately, the goal of acupuncture is to reduce the headache frequency and severity. In migraine patients with temporal throbbing quality, excessive Yang exists with a deficiency of Yin. In order to rebalance the Yin and Yang, the practitioner should supplement the Yin by tonifying the Yin acupoints in the foot (Sanyinjiao SP 6 and Taichong LR 3), and eliminate the excessive Yang by draining Yang points in the head (Taiyang, Extraordinary Meridian Head-and-Neck Point 5, EX-HN 5) and hand (Hegu LI4). Stimulation of the Yin points will soothe the patient, reduce the anxiety and improve sleep. Suppression of the Yang points will relieve the acute headache. Needling of the Ashi points in the head may also suppress the pain.

## Migraine

Among the clinical trials in the Cochran review,<sup>[81]</sup> 16 trials were conducted on migraine patients. Eleven migraine trials compared the effectiveness of "true" acupuncture and "sham" acupuncture. The number of days with headache, frequency of attacks, and attack intensity were compared. Most trials reported differences in favor of acupuncture for at least one outcome. In five trials, the acupuncture group did significantly better than the sham group. Three showed trends in favor of

acupuncture. Two trials found no significant difference between true and sham acupuncture. The remaining one trial was inconclusive due to the high dropout rate during the study. Overall, the majority of the migraine trials showed at least a trend in favor of true acupuncture. One of the sham-controlled studies was done by Vincent.<sup>[29]</sup> They studied patients with chronic migraine though exact diagnostic criteria were not specified. Thirty patients were randomly divided into true acupuncture and sham acupuncture group. Needles were inserted into the classical acupoints with defined depth (1 to 2 cm) in the treatment group but only 2 mm depth at the nonacupoints in the sham group. Because the acupuncture practitioner was experienced and difficult to blind, the author described the design as a single-blinded, randomized controlled trial. A four-week baseline period was followed by 6 weekly treatments and an initial 6-week follow-up period. Further follow-ups were carried out at 4 months and 1 year posttreatment. Headache diaries and analgesic intake records were kept throughout the baseline, treatment and the initial 6-week follow-up period. In addition, headache diaries and analgesic intake records were kept for 2 weeks at 4-month, and 2 weeks at 1-year follow-up. Both groups achieved reduction in weekly pain score and numbers of analgesic intakes after the treatment, compared to the baseline. However, the true acupuncture group achieved a significantly greater reduction in pain score than the sham group (48% vs. 14%). The treatment group tended to use less analgesic medications (38% vs. 28%) but the result did not reach the statistical difference due to the small sample size. The improvement in pain from the treatment group remained substantially better than the control group at 4-month and 1-year follow-ups, although the difference failed to reach significance, again due to inadequate sample. Another randomized placebo-controlled study on 30 migraine patients was done by Ceccherelli and Ambrosio.<sup>[82]</sup> Both acupuncture and acupuncture placebo groups received weekly treatment session for 10 weeks. At the end of the treatment, the acupuncture group achieved 84% of pain reduction compared to the baseline ( $P < 0.001$ ), and the placebo group 50% (nonsignificant). The pain reduction in these groups was not compared for statistical difference. Patients with greater than 50% pain reduction at the end of treatment in both groups were followed; the therapeutic result seemed to last longer in the acupuncture group (average 13 months) than the placebo group (average 3 months). Again, no statistical comparison was done.

A randomized study was recently done to compare acupuncture with flunarizine in the prophylactic treatment of migraine.<sup>[69]</sup> One hundred and sixty women who met IHS migraine diagnostic criteria were randomly divided into acupuncture and drug therapy group, without using sham acupuncture control. The acupuncture group received weekly treatment session for the first 2 months and then once a month for the next 4 months. The drug group received daily flunarizine for the first 2 months and then once a month for the next 4 months. Both group achieved significant reduction of migraine frequency and symptomatic analgesic intake after the treatment. However, the number of migraine attacks per month was significantly lower in the acupuncture group than in flunarizine group at 2- and 4-month follow-up (2.95 vs. 4.10; 2.30 vs. 2.93). The number of analgesics used was also significantly lower in acupuncture group at 2-month follow-up (5.13 vs. 6.7). The total number of patients reporting side effects was significantly lower in acupuncture group than in flunarizine group (10/77 vs. 29/73). Additional study comparing acupuncture with ergot plus caffeine also showed significantly better outcomes in acupuncture group regarding reduction in headache severity and frequency.<sup>[83]</sup>

## Tension-Type Headache

The role of acupuncture in tension-type headache is unclear. In the same systemic review by Cochrane Collaborative,<sup>[81]</sup> results of four sham-controlled trials were evaluated. Acupuncture was found to significantly improve the headache indices compared to sham acupuncture in one trial. One study reported no significant differences between acupuncture and placebo, but the reviewers felt there was a trend favoring acupuncture in reducing the headache frequency and medication use. The result of the remaining studies was uninterpretable due to either lack of actual data, or the large baseline difference between the treatment and control groups and too small a sample size. A randomized placebo-controlled crossover design study evaluated 18 patients with chronic tension-type headache (CTTH) recruited by neurologists.<sup>[70]</sup> The diagnostic criteria used were not described. After a 3-week baseline period, patients were randomized into two groups. Patients received either 3 weekly session of true acupuncture or sham acupuncture followed by 3 weeks of observation before being crossed over for the next 3 weekly session of treatment using the other type of acupuncture. Both the real and sham acupuncture achieved significant reduction of period index score which measured the pain relief. However, the true treatment group did significantly better than the sham-needling group. White and colleagues completed a multicenter randomized controlled trial on 50 patients who met the diagnostic criteria of IHS for episodic tension-type headache (ETTH).<sup>[84]</sup> Patients received either acupuncture treatment or sham procedure weekly for 6 weeks, followed by once a month follow-up for the next 2 months. Patients in the acupuncture group reported a significantly lower headache pain score during the treatment period, compared to the sham group. The follow-up at 2 months tended to favor the true acupuncture but slightly missed statistical significance. A randomized, placebo needle controlled study of 69 patients with either ETTH or CTTH was done by Karst et al.<sup>[85]</sup> Patients were diagnosed using IHS criteria and the practitioner was not blinded. Patients received treatment 2 times per week for 5 weeks. With respect to headache pain score and frequency, both the real and placebo acupuncture groups achieved significant decreases immediately, 6 weeks and 5 months after the treatment. There was no appreciable difference between these two groups. However, there was a significant improvement in the quality of life parameters (clinical global impressions, Nottingham Health Profile) after the true treatment, compared with sham placebo. In another controlled trial, 30 patients with tension-type headache diagnosed according to IHS criteria and demographically matched entered the study.<sup>[28]</sup> After a 4-week baseline period, they received either the true or sham acupuncture once a week for 8 weeks, and followed up at 1, 6, and 12 months thereafter. The sham needles were inserted 2 to 4 mm into the nonacupoints in the same body regions. Compared to baseline, at 1 month after the end of treatment and for the 12-month follow-up, the frequency of headache, analgesic consumption and the headache index in both groups significantly decreased over time; Although no difference was detected, the real acupuncture group exhibited a trend favoring a better outcome than the placebo needing, with 44.3% versus 21.4% decrease in headache frequency, 58.3% versus 27.8% in headache index, 57.7% versus 21.7% in analgesic intake. When the sample size is increased, the likelihood of detecting the significant difference between these two groups should increase.

## Cluster Headache

No randomized controlled trial of acupuncture in the treatment of cluster headache can be found in Pubmed search. A few case reports documenting the benefit of acupuncture in the treatment of cluster exist. Gwan reported a single case treated by acupuncture.<sup>[86]</sup> The patients had at least 8-year history of chronic cluster headache and failed the conventional medical treatments. After

receiving a total of 13 weekly session of acupuncture treatment, the patients remained headache free in the next 3-month follow-up. The long-term benefit was unknown. Dana recently reported another case with multiple daily cluster headaches despite the continuous use of prednisone, verapamil, and oxygen for 2 years.<sup>[71]</sup> After five biweekly acupuncture treatments, the patient successfully weaned off all the medications and remained headache free for 8 months. Over the next 2 years, the headache occasionally recurred, which was well controlled by the combination of rofecoxib and acupuncture. In a small controlled trial, the effect of acupuncture on the CSF met-enkephalin levels and beta-endorphin levels was studied.<sup>[75]</sup> Seven patients with ongoing cluster headache cycle received at least 5 weekly acupuncture treatments for headache. CSF samples were collected 1 week prior to the treatment as the baseline, and within 60 minutes after the 3rd acupuncture. Compared to samples from the age-matched healthy volunteers, there were significantly lower CSF met-enkephalin levels in the cluster patients. The levels were significantly raised after the acupuncture treatment. The CSF beta-endorphin levels of headache sufferers were no different from the controls and were unchanged after acupuncture treatment. Only 2 out of 7 patients reported decrease of either headache frequency or severity that started the third treatment session. Considering the episodic nature of cluster headaches, these case reports bear little significance.

## Other Types of Headache

Two studies have been reported on the effect of acupuncture on supra-orbital headache.<sup>[87,88]</sup> Due to methodological problems-lack of control groups, inconsistent diagnostic criteria, and retrospective design-the overwhelmingly positive benefits of these studies are suspect.

## Adverse Effects of Acupuncture

One of the advantages of using acupuncture is the relatively low incidence of side effect, compared to the other treatments for the same condition.<sup>[3]</sup> However, as an invasive procedure, adverse events do occur and should be recognized by the practitioner. When needles are incorrectly placed, the potential for adverse events increases. Patients should be informed of the potential risk of this technique before treatment. In White's survey of 78 acupuncturists involving 31 822 consultations, a total of 2178 adverse events were reported for an incidence of 684 per 10 000.<sup>[89]</sup> The most common side effects included bleeding, needling pain, aggravation of symptoms, and aggravation followed by resolution of symptoms. The side effects of acupuncture can also be divided into severe and minor categories. The less common but severe side effects include infection, and tissue and organ trauma. When the acupuncture needle is used repeatedly or inappropriately, acupuncture can carry the risk of infection. Practitioners should use sterile disposable, single-use needles. In Norheim's survey involving over 1200 physician and nonphysician acupuncturists,<sup>[90]</sup> the reported infections, in the order of incidence were local skin infection, perichondritis on the auricle, arthritis, and osteomyelitis. Transmission of AIDS and hepatitis have also been reported.<sup>[91]</sup> Pneumothorax is the most frequent serious complication in the category of organ trauma.<sup>[91]</sup> Thirty-five cases of pneumothorax were reported in Norheim's survey.<sup>[90]</sup> Among those more common but minor side effects, fainting during the treatment is the most commonly encountered condition, followed by increased pain and nausea and vomiting.<sup>[90]</sup>

## Contraindications

In general, acupuncture is a safe procedure. There are a few contraindications to the use of acupuncture.<sup>[91,92]</sup> It is recommended that acupuncture applied with electrical stimulator (EA) should be avoided in patient with cardiac pacemakers. Obviously, acupuncture should also be avoided to those with skin and soft tissue infections, bleeding disorders, or patients on anticoagulants. It is not recommended in infants or children, though there is no specific age cutoff.

## Pregnancy

Acupuncture has been used to treat nausea and vomiting associated with early pregnancy,<sup>[93-95]</sup> and is considered safe,<sup>[95]</sup> though there are few data regarding the safety of using acupuncture for headache in pregnant women. Acupuncture practitioners should know that certain acupoints, such as LI4 and SP6, are contraindicated for pregnant women<sup>[13]</sup>; LI4 and SP6 are otherwise commonly used acupoints for headache management.<sup>[69,83,96]</sup> These two points may be used to assist induction of labor at term and preparation of first trimester abortion due to their purported effect on the cervix.<sup>[97,98]</sup>

## Potential Interaction with Medications

Sixteen drugs have been reported to be able to mediate the analgesic effect of acupuncture, especially, electroacupuncture analgesia (EAA).<sup>[99-108]</sup> Most of these experiments were done using the animal models. Among them, meperidine, metoclopramide, and doxepin potentiate EAA<sup>[99,107]</sup>; promethazine, propranolol, and dexamethasone attenuate the EAA.<sup>[102,106,108]</sup> The listed drugs are frequently used in the headache management.<sup>[109]</sup>

## Research

In response to the dramatic growth in alternative/complimentary medicine in the United States, the NIH has set up the Office of Alternative Medicine to oversee the development of this field. Each year, over 10 million dollars in grants are awarded in sponsorship of alternative medicine research, including acupuncture.<sup>[2]</sup> To meet current research standards, NIHCDP recommended clear guidelines be established regarding enrollment procedures, eligibility criteria, diagnostic methods, and study design.<sup>[3]</sup>

## Design Difficulties

Both published studies and clinical experience suggest that patients may respond to acupuncture, but some of the clinical research has demonstrated the opposite.<sup>[3]</sup> The paradoxical outcome may reflect the state of the research. At least two difficulties exist in the design of acupuncture research. The first difficulty is how to select a control or comparable standard. There is urgent need to set up a universal control method in the clinical study of acupuncture. Currently, three approaches are used in the acupuncture headache research. In the first trial design, patients in the acupuncture treatment

group are either compared to no control or those in an untreated group (waiting-list).[87,88] This design may demonstrate that acupuncture treatment is better than not doing anything, but cannot discriminate this effect from placebo or other nonspecific treatment effect. From research standpoint, this type of design is of little value. The second design compares acupuncture to the nonneeding treatment modalities such as transcutaneous nerve stimulation, drug, and physiotherapy.[69,110,111] The research result can show whether the efficacy of acupuncture is comparable to the other proven treatment options, but does not address the question whether needle insertion and manipulation (ie, sham needle control) can invoke comparable antinociception. The FDA may be more interested in comparing the effect of acupuncture treatment to other treatment options.[3,10] Sham-needling is the third control design and is considered a gold standard to scientists who investigate the theoretical mechanism of acupuncture. Sham acupuncture is the technique that does not stimulate known acupoints.[3] The sham needles can be placed in nonacupoints. A modified type of sham acupuncture, "mini" sham needling seems to be a more acceptable and credible control condition; With this technique, the sham needle is inserted 1 to 2 mm into the skin and away from the acupoint.[29,112] This procedure minimizes the needling effect but maintains the psychological impact,[112] and it is felt that the differences between the groups may be attributed to specific treatment characteristics rather than nonspecific psychological (placebo) factors.[29] The adequacy of the control condition can be further confirmed by observing no difference between true and sham acupuncture groups, in how each group perceives the credibility of their treatments.[29,85]

In addition to the selection of controls, how to maintain double blinding is the second research difficulty. Because the performance of acupuncture requires skill and training, it is difficult to "blind" the practitioner.[29,85] The practitioner will know whether he is doing true acupuncture versus placebo acupuncture in the study subjects. Thus, single-blinding of study subjects without blinding the practitioner may be more practical.[112] Some authors still consider their studies as "double-blinded" when both the patients and *evaluating* physicians are blinded, but not the actual acupuncture performer.[25,28] Another point is that patients who have received acupuncture treatment in the past may know whether they are receiving true or sham treatment in the study. Recruiting acupuncture-naïve subjects precludes this design flaw.

## Conclusion

Despite preliminary research evidence suggesting acupuncture may suppress nociceptive TNC and spinal DH neurons via modulation of the release of neuropeptides and neurotransmitters, the exact mechanisms by which acupuncture relieves the headache are not fully understood. Empiric evidence and results of clinical investigations suggest that acupuncture may be a promising treatment option in the treatment of headache, especially migraine. Acupuncture is a safe and minimally invasive procedure, and may specifically benefit those patients who can not tolerate headache medications. Further well-designed acupuncture studies should illuminate acupuncture's analgesic mechanisms and value in managing various headaches.

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