

Mechanisms of Acupuncture Analgesia: Effective Therapy for Musculoskeletal Pain?

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Acupuncture (AP) is effective for the treatment of postoperative and chemotherapy-induced nausea/vomiting and for postoperative dental pain. Several recent randomized trials have provided strong evidence for beneficial AP effects on chronic low-back pain and pain from knee osteoarthritis. For many other chronic pain conditions, including headaches, neck pain, and fibromyalgia, the evidence supporting AP's efficacy is less convincing. AP's effects on experimental pain appear to be mediated by analgesic brain mechanisms through the release of neurohumoral factors, some of which can be inhibited by the opioid antagonist naloxone. In contrast to placebo analgesia, AP-related pain relief takes considerable time to develop and to resolve. Thus, some of the long-term effects of AP analgesia cannot be explained by placebo mechanisms. Furthermore, it appears that some forms of AP are more effective for providing analgesia than others. Particularly, electro-AP seems best to activate powerful opioid and non-opioid analgesic mechanisms.

Introduction

Acupuncture (AP) is an ancient Chinese healing art used for the treatment of pain for nearly 3000 years [1]. De Qi (pronounced "Chee") or life energy is the most important concept of traditional Chinese AP and is assumed to flow through the body in so-called meridians. Illness is thought to be related to imbalanced energy flow, and treatments attempt to manipulate this flow at specific AP points to restore the normal energy balance and thus the patient's health. Traditionally, many AP points are thought to be linked to each other by meridians; however, the anatomic

existence of meridians or AP channels is unclear. Also, no conclusive evidence has ever demonstrated any anatomic structure consistent with meridians [2]. Although most of their length can be contained within a single dermatome, all meridians eventually associate with two or more dermatomes. Thus, a system of interconnecting neurons within the spinal cord is more likely to explain the trans-segmental nature of sensation propagated along a meridian [3]. Although AP points are often associated with nerves, blood, or lymphatic vessels, meridians do not conform to any one of these structures [4].

The role of specific AP points for different treatment modalities is controversial [5], but for effective AP analgesia, only the stimulus mode and not specific locations appear to be important [6]. However, for treatment of local pain (eg, back pain) needling of affected tissues has shown some clinical benefit [6]. AP points can be manipulated in several different ways, including manual needling, electrical stimulation (electro-AP), heat (moxibustion), pressure (acupressure), and laser energy. Traditionally, specific treatment modalities have been selected based on diagnostic findings including the patient's appearance, pulse, and smell. Many AP treatment modalities, however, are difficult to study in controlled trials. Thus, results from many AP trials have raised methodologic concerns due to lack of standards. The exceptions are trials using manual needling and electro-AP, which can be well standardized for animal or human experiments. These forms of stimulation represent the most reliable methods for the study of AP-related analgesia.

Usefulness of AP in Western Medicine

A recent search of Medline databases showed approximately 12,000 articles relating to AP, indicating that complementary and alternative medicine (CAM) has become very popular in Western countries [7].

According to a nationwide government survey released in 2004, 36% of US adults aged 18 years and over use some form of CAM [8]. According to this survey, Americans are most likely to use CAM for back, neck, head, or joint aches or other painful conditions. More than 20%

of the UK population uses CAM each year, and 47% will try CAM at some point in their lifetime [9]. AP is one of the most popular and widely used CAM interventions for pain [10], particularly for the treatment of osteoarthritis (OA) [11]. Of all visits to CAM practitioners in the UK, 71% are due to musculoskeletal problems [9]. An estimated 8.2 million US adults have used AP in the past, and 2.1 million have used it in the previous year [8].

AP has well-documented therapeutic effects for several clinical pain conditions, but it is often dismissed by mainstream allopathic medicine because of sometimes inconclusive data regarding its superiority to placebo. In 1997, the US National Institutes of Health convened a Consensus Development Panel on AP. The Panel Report was released in 1998 and reported Level 1 evidence for AP's efficacy on nausea and vomiting (postoperative and chemotherapy) and postsurgical dental pain [12]. Much less convincing evidence was found for other conditions such as addiction, stroke rehabilitation, headache, menstrual cramps, carpal tunnel syndrome, and asthma. Since then, many additional AP studies have been published to support at least some of these conclusions. In general, however, the clinical trial experience of AP analgesia for most chronic pain conditions has been disappointing.

Problematic Trial Design

Concerns about AP studies are numerous and relate to inadequate trial design, including small sample sizes or lack of control conditions. Methods most frequently used for AP studies include comparing needling with a) no treatment or waiting list for treatment (natural history), b) sham AP (insertion of needles away from AP points), c) placebo AP (no needle penetration of the skin), or d) a commonly used, effective biomedical treatment. Although the last represents an especially challenging trial design, it allows clinically relevant head-to-head comparisons. Also, many different methods of needling are frequently used. Therefore, it comes as no surprise that the analysis of many treatment studies did not confirm AP to be more efficacious than placebo [13]. Thus, standardization of trial designs would be very helpful for future AP treatment evaluations and would make subsequent meta-analyses more feasible.

Challenges Related to AP Pain Trials

The efficacy of AP has been assessed for several acute and chronic pain conditions. AP interventions for acute pain are challenging, because they have to exceed such unspecific effects as natural history and regression to the mean. Despite such challenges, AP analgesia has been shown to exceed placebo effects during and after dental surgery [14]. Although regression to the mean also plays an important role in chronic pain studies, here the natural history is less predictable but still may affect the

outcome. Meta-analyses of AP trials for several chronic pain disorders, including neck pain [15], headaches [16], and fibromyalgia (FM) [17], have generally been negative, perhaps because of trial design problems [18–20].

AP Effects on Neuroendocrine Mechanisms

In addition to trial design, several different stimulus modalities including manual and electro-AP contribute to the variability of AP studies. Electro-AP seems to recruit different brain mechanisms [21] and is more effective in increasing experimental pain thresholds in humans [22] than manual AP. Importantly, AP analgesia takes considerable time to reach maximal effectiveness (up to 45 minutes) and to dissipate [23]. Much evidence indicates that neuroendocrine factors related to AP analgesia are not released at the AP site but rather at specific areas of the central nervous system [23]. In rodents and humans, the pain relief produced by focal electrical stimulation of the periaqueductal and periventricular gray areas of the brain involves a neuroendocrine pain inhibitory system similar to AP analgesia. Both forms of analgesia take some time to develop and resolve. The activity of this neuroendocrine system can be antagonized by depleting analgesic neurotransmitters with specific antibodies and by the narcotic antagonist naloxone. In addition, tolerance to analgesia develops not only to prolonged brain stimulation but also to AP, and both show cross-tolerance with morphine.

The immediate and cumulative effects of electro-AP on chronic visceral pain can be studied in rats using irritable bowel syndrome as a model. Electro-AP attenuated rats' increased abdominal withdrawal reflex and the heightened activity of their abdominal muscles during rectal distension [24]. Repeated electro-AP treatment for 2 weeks showed that those effects appeared 2 to 4 days after the first electro-AP session, reached a maximum within 8 to 12 days, and lasted for at least 5 days after electro-AP treatment was stopped. These data provide evidence that electro-AP can effectively reduce visceral pain of animals and thus may also be useful for the treatment of chronic visceral pain in humans.

Neuromodulatory Mechanisms of AP Analgesia

Most AP studies reporting substantial experimental pain reduction used electrical needle stimulation. Typically, electro-AP studies utilize needle insertion points according to well-established guidelines [25]. AP needles are inserted 1.5 to 2 inches into tissues and high-intensity current (10–50 mA) is passed through the needles at low frequencies (4–7 Hz) using short biphasic pulses (duration, 0.1 millisecond). The current is usually increased to a point where any further increase is described as uncomfortable by patients. Electro-AP treatments commonly last for 25 to 30 minutes and are given on a weekly basis.

Analgesia usually peaks within the first 2 hours after AP treatment and thereby is suggestive of a neuromodulatory mechanism of action. Also consistent with such a mechanism are the long delays to maximum effect, the generalized spatial extent of the analgesia, and the long duration of the effects. A neurohumoral mechanism also is supported by studies which demonstrate that human spinal cerebrospinal fluid endorphins and dynorphins increase after AP and during the period of analgesia [26]. This release of endogenous opioids coincides with AP analgesia and can be potentiated by preadministration of D-phenylalanine, which inhibits enkephalinase-mediated degradation of enkephalins and endorphins [27]. Furthermore, several studies have shown that the opioid antagonist naloxone can reverse or antagonize AP analgesia in animals [28] and humans [29].

Role of Peripheral and Central AP Mechanisms

An acute painful stimulus can be used to alleviate ongoing pain and is known as counter-irritation. This concept shares common features with AP and transcutaneous electrical nerve stimulation (ie, application of somatic stimuli, either noxious or innocuous, to obtain pain relief). During classical Chinese AP, the site of treatment in relation to the painful area is highly variable, ranging from the painful dermatome itself to often distant AP points. The relevance of specific AP for analgesia is controversial [5]. However, some studies showed superior analgesia if AP points were used compared to sham AP points [30]. Whereas central pain inhibitory mechanisms are clearly important for electro-AP [31], local effects also must be considered [23]. A novel use of AP in patients with chronic low back pain showed simultaneous effects of AP on experimental heat pain and clinical back pain [6].

Several lines of evidence indicated that the observed analgesia was not the result of patients' expectations or biases, but reflected a central neurohumoral mechanism with delayed-onset characteristics. First, pain reduction occurred for clinical pain in an area proximal to the AP needles (low back region) and for cutaneous heat pain at a distal area (forearm). Second, the magnitudes of the effects on experimental pain were the same as those found for clinical pain. Third, peak analgesic effects from electro-AP did not occur immediately but 1 to 2 hours after treatment. Finally, the magnitudes of these analgesic effects were not correlated with patient expectation ratings. In addition, although electro-AP reduced these patients' chronic back pain for several days, it did not change their responses to experimental pain that had been applied to the forearm. Such a pattern indicates that the treatment had direct or indirect effects on the tissues from which the nociceptive input originated. Some of the possible mechanisms for this local effect include reflex relaxation of muscles induced by intense stimulation of

trigger points [32]. For example, if AP reduces low back pain by an endogenous opiate-like mechanism, this effect might allow the patient to engage in increased physical activities, which may have a therapeutic effect on peripheral pain input, thus reducing chronic pain. Therefore, centrally mediated initial analgesic effects of AP do not exclude subsequent peripheral therapeutic changes that may take place over time.

Role of Psychological Factors for AP Analgesia

Patients' desire and expectations about pain relief can influence the analgesic effects of any intervention and are responsible for placebo analgesia [33]. However, little evidence has shown that AP analgesia is prominently mediated by factors such as stress or placebo effects. Particularly the spatial and temporal features of AP analgesia seem to preclude a substantial role of such factors. In contrast to the immediate effects of stress and placebo on pain, AP analgesia is delayed by up to 24 hours to maximum effect, and can last for days after a single treatment [34]. In addition, several studies have shown that placebo effects on experimental pain can be predicted by expectations [33]. However, at least one study has demonstrated that patients' expectations for chronic pain relief were not correlated with the magnitude of AP analgesia [6].

Effects of Expectations on AP Analgesia

Convincing evidence from multiple studies has shown that expectations can modify pain perception [35,36]. Several lines of research indicate that expectations associated with the application of placebos can activate endogenous analgesic systems, related to opioid and nonopioid pathways [35,36]. Functional MRI studies have shown decreased activity in pain-sensitive regions related to placebo application [37,38]. The activation of limbic structures influences affective elements of pain perception [39]. Thus, depending on the individual patient, the framework of AP could be associated with strong expectation and placebo effects [20].

However, only a few studies have investigated the impact of expectations on AP analgesia. The expectations of patients undergoing either real or sham AP during dental surgery significantly predicted pain levels afterwards, independent of AP type [40]. Investigators obtained similar results using positron emission tomography in a study of patients with OA [41]. The study showed that AP, expectancy, and beliefs modulated the activity of the limbic system [41].

In several AP trials, the attitudes of OA patients regarding AP were found to be highly positive in general, and individual patients' expectations of AP were high [42]. In a pooled post-hoc analysis of these trials, OA patients with high expectations were much more likely to report better outcomes than patients with lower expectations,

both after treatment and several months later. The impact of expectations on study outcomes was large and thus clinically relevant. This effect was observed in patients on both real and sham AP. In the pooled analyses, significantly more treatment responders could be detected in the AP group than in patients receiving minimal AP; however, this effect was lost at follow-up.

Neuroimaging of AP Analgesic Effects

Functional brain imaging studies of AP analgesia on experimental pain have been conducted with animal [43] and human subjects [44]. In rats, AP resulted in increased brain activity of the hypothalamus dependent on the extent of stimulation, whereas in human subjects, AP dramatically increased activation of the periaqueductal gray matter. In general, electro-AP, mock electro-AP, minimal AP, and sham electro-AP on either real AP points or non-AP points elicited significant activation of multiple brain areas of healthy human volunteers, including the hypothalamus, primary somatosensory cortex, and rostral anterior cingulate cortex. The superior temporal gyrus and medial occipital cortex seems to respond to minimal electro-AP, both sham and real [45].

Current Evidence for AP Analgesia

Animal research provides strong support for long-lasting AP analgesic mechanisms that are at least partially mediated by opioidergic and/or monoaminergic neurotransmission involving the brainstem, thalamus, and/or hypothalamic and pituitary regions [46]. The prolonged duration of AP analgesia is one of the strongest arguments for specific needling effects, because placebo analgesia is generally considered to be brief. Neuroimaging studies in human subjects have shown that AP modulates a widely distributed network of brain regions predominantly involved in pain perception including limbic areas, sensorimotor and prefrontal cortices, brainstem nuclei, and the cerebellum. Many of these networks also support placebo analgesia. Activation of some brain areas (dorsolateral prefrontal cortex and anterior cingulate cortex) seems to indicate placebo mechanisms, whereas others (amygdala, insula, and hypothalamus) appear to demonstrate AP specificity [47]. AP seems to elicit greater brain responses within the ipsilateral insular cortex than sham AP [41], suggesting AP specificity. Other differences between true AP and sham AP include dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and midbrain activations. However, additional studies of true and sham AP are required to clearly dissociate between specific and nonspecific placebo or nocebo effects. Spinal gating, stress-induced analgesia, and diffuse noxious inhibitory control may be responsible for short-term analgesic effects [48].

The approach and methods taken in most AP studies of chronic pain do not appear to be sensitive enough to

detect possible analgesic effects. Thus, the use of additional methodologies, including psychophysical tests that can detect central and peripheral analgesia, appears to be useful. Particularly, magnitude matching of experimental pain with clinical pain could provide a successful approach for the assessment of AP analgesia during chronic pain trials [6]. Such methods could help determine how much a given form of pain therapy reduces the sensory and affective dimension of pain and the extent to which this analgesia is peripherally or centrally mediated. Furthermore, research must precisely characterize AP analgesia time course and duration. Otherwise, imprecise analgesia assessments could confound the magnitude of pain relief and result in negative AP trials.

The available evidence allows the conclusion that AP is effective for the treatment of two clinical conditions (postoperative and chemotherapy-induced nausea and vomiting and postoperative dental pain), and some data indicate that AP may be useful to treat several chronic pain conditions, including headache, chronic low back pain [49], and pain related to knee OA. In contrast, no evidence exists to show that AP is effective in treating addiction, insomnia, obesity, asthma, or stroke deficits. However, the absence of evidence is not evidence of its absence. Most meta-analyses of AP chronic pain trials reported lack of well-designed studies [50], thus effectively precluding a definitive answer about the usefulness of this treatment. Future AP trial designs, however, would benefit from standardization, including number of AP points selected, frequency and duration of treatments, and whether or not de Qi should be elicited [51]. Most importantly, it appears that not all forms of AP are equally effective for analgesia. Electro-AP seems to best deliver stimuli that activate powerful opioid and nonopioid analgesic mechanisms. Thus, properly designed double-blind, controlled trials using adequate electro-AP may vindicate this treatment for many chronic pain conditions including FM, irritable bowel syndrome, and low back pain.

AP Effects on Clinical Pain

Many studies have examined the effect of AP on clinical pain [20]. Because biomedical therapies often provide only small improvements for chronic pain syndromes, these conditions may benefit from the addition of safe and effective treatments and are therefore particularly promising targets for AP analgesia. Although AP seems to be effective for several types of chronic pain, including neck pain [52], back pain [53], migraine [54], and FM pain [55,56], these findings are controversial and were not confirmed by several recent studies [49,57,58,59•].

When the methodologic quality of more than 50 randomized controlled trials of AP for chronic pain was examined, two thirds of these trials received only low-quality scores [60]. Furthermore, an important association between study quality and study outcome

could be observed. Low-quality studies reported significant analgesia more frequently than high-quality trials, which raises concerns of inflated effect sizes from methodologic problems. However, even many high-quality AP studies had apparent trial design problems. These trials often used comparisons between real and sham AP analgesia. Although sham AP is considered a placebo, systematic reviews indicate that the proportion of participants improving in the sham groups is significantly higher than in the inert placebo groups [60]. This finding may be due to chance or an unknown confound, but one must at least consider that sham AP is not a physiologically inert placebo and may produce nonspecific analgesic needling effects [61]. Because the mechanisms of AP and placebo analgesia are different, future studies should be designed specifically to separately characterize these effects.

Thus the efficacy and the mechanisms of AP analgesia for chronic pain syndromes remain unclear despite many years of research. However, considerable evidence suggests that AP can reduce experimentally induced pain [6], yet this effect is sometimes small and/or inconsistent [62]. Extensive experimental evidence seems to indicate that the analgesic effects of AP are mediated by an endogenous opiate-like mechanism [63], although not all analgesic effects can be reversed by the opioid antagonist naloxone [64].

AP Effects on Chronic Pain

There is convincing evidence from randomized controlled trials of AP in patients with migraine [65], tension-type headache [66], chronic low back pain [67], and knee OA [68,69] comparing minimal AP (superficial needling at non-AP points) with waiting list controls showing large effects of both AP and minimal AP. However, only in patients with OA did the trials show significantly greater effects of AP over minimal AP for the main outcome measure [68,69].

AP for Low Back Pain

For treatment of acute low back pain, AP data are sparse and inconclusive. Recent trials, however, seem to favor AP's short-term analgesic effectiveness for chronic low back pain compared with most other therapies. A large observational AP study of routine care in Germany corroborates findings from other randomized trials suggesting that patients with chronic low back pain benefit from treatment with AP [70]. Furthermore, the presence of depression did not seem to influence AP effects on low back pain. The main analysis included more than 2500 patients treated by 1607 physicians. After 6 months, 45.5% of patients with low back pain demonstrated clinically significant improvements in their functional ability scores. The mean number of days with pain was decreased by half (from 21 to 10 days/month). Employed patients reported a 30% decrease from baseline in days of work

lost. Only 8.1% of patients experienced adverse events, most of which were minor. Subgroup analyses focusing on pain severity, illness duration, and depression revealed statistically significant relationships with baseline measures and pain reductions after AP. These benefits seemed similar for all participants, regardless of duration or severity of their low back pain.

A recent meta-analysis of AP trials for chronic low back pain was also supportive of relevant AP effects on this chronic pain condition [50]. This meta-analysis showed that AP was significantly more effective than sham treatment (standardized mean difference = 0.54, 95% CI, 0.35–0.73) for short-term relief of chronic pain. Recent evidence also seems to support AP's effects on chronic low back pain for up to 2 years [71].

AP Analgesia for Knee Pain from OA

Accumulating evidence suggests that AP is an effective therapy for pain from knee OA, lasting for at least 26 weeks. Whereas a previous review of seven AP trials for OA knee pain alluded that AP might play a beneficial role in its treatment [72], a recent review demonstrated evidence that AP was superior to sham (or placebo) AP for treating chronic knee pain, both in short and long term [73••]. These results relied mostly on high-quality studies of sufficient size from different research groups (see later discussion). Importantly, AP was superior to usual care for both pain and function.

One of these studies—a large, well-designed, sham-controlled trial of AP for OA pain of the knee—showed that active treatment was significantly better than sham therapy for both pain and disability [68]. Two additional high-quality studies strongly support this conclusion [74,75]. However, a recent AP trial of pain from knee OA was found to be negative for improvement in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain at 6 months [76]. Several other outcome measures seemed to favor AP compared to sham, including most WOMAC subscales and the patients' global assessments at 3 and 6 months. In general, AP seems to have large overall effects on knee pain (Cohen's $d = 0.8$), despite being only minimally superior to sham AP [77••,78••]. One explanation may be the fact that sham AP has placebo effects, as consistently demonstrated by trials of OA knee pain [76], migraine [65], neck pain [79], and back pain [67].

Investigators recently tested whether AP effects observed in randomized controlled trials differ from those seen in clinical practice [68]. During a randomized controlled trial of AP for knee or hip OA pain, patients could opt for additional treatments not determined by the study protocol. The effects of AP on OA pain, however, were not affected by this study design.

Although patients receiving AP for knee OA report improved quality of life (QOL), this treatment is associated with higher costs compared with routine care,

primarily due to AP expense [80••]. However, small cost increases related to AP may be offset by improved QOL reported by OA patients after AP therapy.

AP Effects on FM Symptoms

Despite widespread pain hypersensitivity, AP is well tolerated by FM patients, and most seem to find participation in AP studies rewarding. However, as with other chronic pain conditions, the lack of standardized AP treatments makes comparisons among FM studies difficult. The outcome measures used to assess clinically relevant endpoints in AP trials have varied among almost all randomized controlled trials. Many investigators use the Fibromyalgia Impact Questionnaire as a disease-specific outcome measure, but this approach is not generally accepted. In addition, although most FM patients receive repeated AP treatments (usually in weekly intervals), the overall duration of randomized controlled trials often varies. Also, AP is frequently evaluated as an adjunct to the usual FM therapy.

Some of the most promising results of AP analgesia for FM pain come from several randomized controlled trials using electric needle stimulation [56,81,82]. In these trials, pain and tenderness of FM patients significantly improved in both AP and sham groups. Despite methodologic differences in needle placement and stimulation, researchers observed statistically significant effects on pain, fatigue, and anxiety, and the AP groups maintained these improvements for at least 1 month after the end of the trials.

In one trial, FM patients were treated with six electro-AP sessions over 3 weeks using five pairs of electrodes for AP-point stimulations [56]. Investigators applied rectangular electrical pulses with frequencies between 1 and 99 Hz. The intensity of the currents was slightly above perception threshold and just below pain threshold. Up to 10 stainless steel needles (0.3 mm by 25 mm, excluding the handle) were implanted at 10 sites depending on the symptoms and pain patterns. A similar number of needles was used for control subjects, but these needles were inserted about 20 mm away from the true AP point (sham). The pain thresholds of patients treated with electro-AP increased by 70%, compared with 4% for those treated with sham procedures. Patients in the electro-AP group reported less clinical pain and required less pain medication than the sham-AP group, but approximately 25% of patients treated with electro-AP did not experience any improvements.

These positive findings are supported by a recently published randomized controlled trial of electro-AP showing significantly improved FM symptoms over placebo [82]. Using the Fibromyalgia Impact Questionnaire as primary outcome measure, all FM symptoms were reported as improved by electro-AP compared to baseline. However, only fatigue and anxiety were statistically different from placebo. Importantly, AP benefits lasted for

at least 1 month after the treatments, but they did not include significant improvements of activity or physical functioning. A recent randomized controlled trial applying classical AP for FM symptoms reported a subset of patients who experienced significant improvements in clinical pain, fatigue, and function. However, the clinical efficacy of classical AP treatments for FM did not seem to depend on sham or true needle placement, suggesting strong placebo effects [59].

Overall, the magnitude of clinical benefits of AP for FM appears to be moderate but similar to that reported with pharmacologic interventions such as tricyclic antidepressants, fluoxetine, and tramadol/acetaminophen. In contrast to regular AP, all randomized controlled trials using electro-AP for FM symptoms were found to be more effective than placebo or sham-AP, suggesting that the latter method may be superior for FM pain.

Conclusions

AP seems to be effective for several chronic musculoskeletal pain conditions, including low back pain and OA of the knee. More evidence, however, is needed to confirm or refute AP's effectiveness for other chronic pain conditions. First, more well-designed mechanistic studies are necessary to evaluate the peripheral and central mechanisms that seem to be important for AP analgesia. These evaluations should not be limited to well-known opioid and stress hormone analgesic mechanisms but also should include assessments of placebo-related factors such as ratings of expected pain reductions, ratings of desire for relief, and conditioning. In addition, new technologies, including functional brain imaging, may contribute information on pain-related brain activations that play an important role in AP analgesia. Functional MRI and magnetoencephalography are increasingly utilized noninvasive measures of pain-related brain activity that have excellent spatial and temporal resolution. These techniques could be used to identify central nervous system responses specific to AP.

Second, well designed and sufficiently powered randomized controlled trials are crucial to provide efficient allocation concealment and avoid selection bias. Such trials can prevent the otherwise frequently occurring biases and overestimation of analgesic treatment effects, which have been reported to exceed 40% in some studies [83].

Third, some chronic pain disorders such as FM may require unorthodox AP needle placements during therapy. In traditional Chinese medicine, so-called Ashi points are commonly used for the treatment of pain originating outside of major meridians. Such an approach utilizes AP needle placement exactly where the pain is felt, regardless of whether pain areas are located on meridians. Because FM is a widespread pain condition, nontraditional AP needle placements, including Ashi points, may be required for more effective analgesia.

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- Of importance
- Of major importance

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