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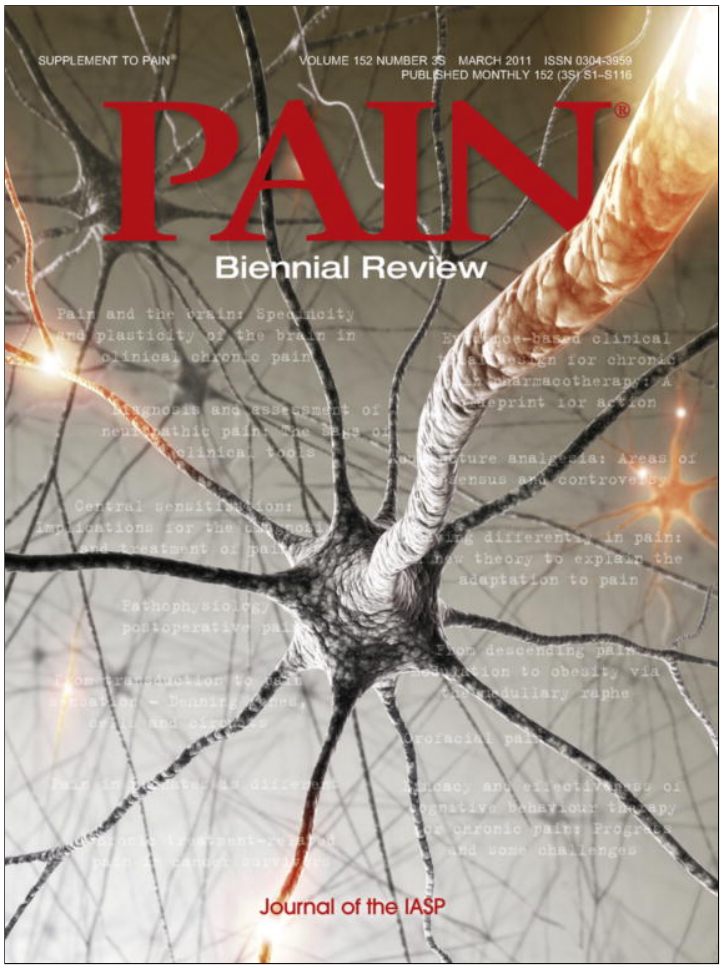

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Review

Acupuncture analgesia: Areas of consensus and controversy

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1. Introduction

The clinical practice of acupuncture is growing in popularity world-wide. In parallel, interest in the scientific basis of acupuncture has been increasing, as reflected by a dramatic rise in the number of scientific publications on acupuncture and related techniques (ART) in the recent decade [16]. After 40 years of extensive studies, compelling evidence has been obtained to support acupuncture as a useful tool for treating a spectrum of diseases. In fact, more than 40 disorders have been endorsed by the World Health Organization (WHO) as conditions that can benefit from acupuncture treatment. Pain is particularly sensitive to acupuncture. As such, in a total of 3975 acupuncture research articles published from 1991 to 2009, 1647 (41%) focus on pain and analgesia [16]. Many comprehensive review articles on acupuncture analgesia have been published in recent years [61,62,72]. In this article, with strict limitation of space, we will concentrate on summarizing the areas of consensus and the controversy stemming from research published in the recent decades on the clinical efficacy and the basic mechanisms of acupuncture. For example, should we mainly use manual needling in clinical trials or could we also use electroacupuncture (EA)? Is acupuncture little more than a placebo effect? Why are there so many negative reports in large scale clinical trials? In clinical practice, should we put emphasis mainly on the specificity of meridians and acupoints, or should we also care about the characteristics of the stimulation? We believe that a timely review is important for guiding future efforts to advance this ancient medical art, utilizing the ever growing modern knowledge and technology, as a beneficial, safe and cost effective option in our global health care system.

2. Acupuncture analgesia, scope of discussion

2.1. Classical acupuncture

The traditional practice of acupuncture is based on the hypothesis that all the body's physiological functions are modulated by 12 bilaterally distributed channels (six Yin and six Yang channels), supplemented by two midline channels (one in the front and the other in the back of the body). Circulating within these channels is the hypothetical "Qi" which regulates the body function. When the flow of Qi is blocked, pain and illness occur. By inserting a needle followed by its appropriate manipulation, one can unblock the channel, thereby re-establishing the free flow of Qi and relieving the pain. These hypotheses, however, have not yet been validated by modern science and technology.

2.2. The evolving technique of acupuncture

The methodology of acupuncture is ever changing along with the development of science and technology. The most ancient way of trying to reopen the blocked channel was to use a sharp stone to press the body near the site of pain ("acupressure", using the current term). Following the discovery of various kinds of metals one can use thick needles made of silver and then fine needles made of stainless steel to puncture the skin for the same purpose. In recent decades, electrical stimulation has often been used to enhance mechanical stimulation (EA), and further, skin electrodes can be used to replace needle penetration (transcutaneous electrical acupoint stimulation, TEAS) for safety and time saving.

2.3. The neural hypothesis for acupuncture action

The search for the anatomical and histological substrate of the "channel" or "meridian" has continued for decades. Evidence for the involvement of the nervous system is sufficient and straightforward. Studies performed in the 1960s in healthy humans showed that manual acupuncture at one point (LI4 at the hand) induced a gradual increase in skin pain threshold that reached a plateau at 30 min, was maintained for at least 50 min, and faded after removal of the needle with a half-life of 15–17 min [45]. This characteristic time-dependent analgesic effect was totally abolished after the infiltration of the local anesthetic procaine deep into the acupoint at the muscle and tendon layer, but not subcutaneously, highlighting the importance of nerve innervations distributed in the deeper structures of the acupoint. The effect was present in hemiplegic patients when the needle was inserted in the healthy side, but was absent in the paralytic side of the body [45]. The results indicated the involvement of peripheral sensory

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nerves and the afferent nerve pathway in the spinal cord. This has been supported by numerous publications using multiple approaches including nerve severance, focal injection of transmitter blockers and focal lesion of the CNS [17,61,72]. It should be pointed out that the pathways of peripheral nerves do not always coincide with that of the "meridians", despite of the fact that many major acupoints are located along the deep nerve tracts, e.g., PC6 with the median nerve, LI4 with the deep branches of median nerve, and ST36 with the deep peroneal nerve. Efforts are also being made to identify novel substrates other than neural pathways for acupuncture related information processing. Among the candidates are collagen fiber bands [1,13] and the Bonghan circulatory system [48,53], but the evidence is not convincing enough to link them to the supposed meridian system.

2.4. Rapid growth of publications on acupuncture and related techniques (ART)

Bibliometric analysis of SCI-expanded publications revealed that the first episode of papers of ART appeared in the 1970's, with an average of 148 papers per year (1973–1997), among which an average of 97 belongs to the category of "articles". A dramatic (over 40%) increase in the number of publications occurred in 1998, with continuation of the trend to reach an annual production of 700 papers (450 articles) in 2009 [16]. What can we learn from this rapid growth of acupuncture related publications, which seems likely to continue in the coming years? Several key points deserve close attention.

3. Controversies in selection of acupoints and control sites for research studies

3.1. Use of TCM principles for selecting acupoints to treat a given disorder

Modern acupuncture researchers usually respect the traditional acupuncturist's decision on where to insert needles. The rationales of the selection, based on theories of traditional Chinese Medicine (TCM), usually cannot be completely understood and explained by modern medical science. In fact, there is a basic difference in the perception of health and disease from the perspectives of Western medicine and TCM. Western medicine's definition for a disease tends to be narrow and quantitative, whereas TCM holds a holistic concept, viewing the disease as a disturbance of the equilibrium among body functions and between the subject and the environment. In order to restore equilibrium, there seem to be at least three principles for choosing the right point(s) to stimulate: (a) "It is more important to identify the right meridian rather than the right point within the meridian", e.g., to use acupoints on the stomach meridian for stomach diseases. (b) "To use the meridian with its pathway reaching the vicinity of the diseased organ", e.g., to use the BL63 point of the urinary bladder meridian on the lateral side of the foot to treat eye disease, since the bladder meridian goes all the way up to the head, reciprocally connected to the inner canthus of the eye (BL1, jingming, meaning "eye clear") [10]. (c) "Where there is pain, there is a transport point", so you can use the "Ah Shi" (Ah, Yes) point where you feel tenderness by finger palpation.

For those who were not trained in TCM, it may not be easy to apply the first two principles since the anatomical substrate for the meridian is still pending. Moreover, the name of the organ for the TCM meridian may not mean the same organ as it is used in Western anatomy today. For example, the lung meridian is related to skin diseases rather than the respiratory system, the kidney meridian is related to genital organs rather than urinary system. Some of the meridians (e.g., the triple energizer) do not even have their anatomical counterparts.

3.2. Neurobiological considerations

Modern neurobiology has provided a number of hypotheses which may be useful to help in choosing the appropriate point to stimulate, although none of them can be regarded as universally applicable. (a) In a recent study Goldman et al. reported that in mice with ankle inflammation, insertion of a needle adjacent to the ankle joint and manipulation once every 5 min for 30 min greatly reduced the inflammatory and neuropathic pain-related behaviors [14]. They attributed this local analgesic effect to the needle trauma-induced local release of adenosine, which interacts with the A1 receptor located on the nearby afferent nerves, thus interfering with the transmission of nociceptive signals. The authors stressed that this is a real "local" effect, since stimulation of the acupoint does not help the problem in the contralateral side or on distant site of the body. (b) The diffuse noxious inhibitory control (DNIC) is another potentially applicable hypothesis [33], although the high-intensity stimulation required for the activation of C fibers contrasts with the findings that acupuncture analgesia is mediated mainly by A_β fibers and part of A_δ fibers [38]. (c) The gate control theory of stimulating the thick fiber to suppress the thin fiber transmission seems to be relevant to both acupuncture and transcutaneous electrical nerve stimulation (TENS) [41], although the requirement of segmental distribution does not readily explain the "distant" principle of acupoint selection. In fact there are numerous studies showing that acupuncture's analgesic effect can reach distant sites. As examples, EA on distal body acupoints can effectively treat tension-type headache [68], and non-segmental acupoint (ST36) stimulation was shown to be as effective as segmental stimulation in suppressing post-operative wound pain, whereas non-segmental non-acupoint shoulder region stimulation was ineffective [66].

3.3. Validation of acupoint specificity for clinical practice

Zhang et al. [70] conducted a systematic review addressing the question "are acupoints specific for diseases?" In 12 clinical trials with sham acupuncture controls on non-acupoints or on irrelevant acupoints, half of the trials had positive results in favor of acupoint specificity. However, not all trials had appropriate design. Among six trials with low risk of bias, five showed no statistically significant difference between proper and sham acupoint treatments. A recent systematic review of clinical trials even concluded that sham acupuncture may be as efficacious as true acupuncture [42]. From a neurobiological perspective, it seems irrational to assume that needling at any place on the body would produce the same effect. Due to the uneven distribution and density of nerve endings in the body, it would be absolutely acceptable to have some points more sensitive than others. For example, the nerve terminals on the lips and the finger tips may be by far more abundant than those on the trunk, as shown by the dramatic topographical difference of the somatic representative areas on the cerebral cortex.

From a developmental biology point of view, pain is the most primitive reaction in response to trauma for self protection; therefore it may be argued that pain modulation may be a relatively non-specific physiological response. In contrast to pain control, acupuncture modulation of gastric motility, for example, seems to be more clear in targeting. It was reported that stimulation at ST36 produced an excitatory effect on gastric motility which is associated with activation of the vagus nerve, whereas stimulation at ST25 produced an inhibitory effect on gastric motility, which is associated with activation of sympathetic nerve activity [27].

3.4. How many acupoints are there on the body surface?

Concerning the total number of acupoints, it was only 160 in the Inner Classic of the Yellow Emperor (Huangdi Neijing, published

between 200 and 100BC) [26], and 349 in the A–Z Classic of Acupuncture and Moxibustion (Zhenjiu Jia Yi Jing, published 300AD) [73], while this number increased to 361 in modern TCM textbooks [57]. However, for the purpose of acupuncture research, the commonly used acupoints are limited to a rather small number. Based on a search on the Science Citation Index Expanded (SCI-Expanded) from 1899 to 2010/7/24, the three most frequently used acupoints are Hegu (LI4, $n = 345$), Zusanli (ST36, $n = 299$), and Neiguan (PC6, $n = 259$). The other three famous acupoints Baihui (GV20, known for psychic disorders), Lieque (LU7, known for neck pain) and Weizhong (BL40, known for waist and back pain) were only used for 34, 10 and 8 times, respectively. Although the frequency of acupoint selection in published studies may not be a realistic reflection of acupoint selection in clinical practice, these figures may suggest that the number of frequently used acupoints could be narrowed down to a fraction of the total of 361.

3.5. How to find a non-acupoint?

Compared to the task of finding an optimal acupoint for a given effect, it may be more difficult to find an inert point serving as the control. According to TCM theory, the body is distributed with 14 meridians (“Jing”, like boulevards), that bear countless branches (“Luo”, like byways). Thus, in theory, it would be hard to find a body site without the influence of any Jing and Luo. Considering that most of the meridians are densely distributed on the extremities, and at the front and the back of the trunk, it might be preferable to locate the lateral side of the trunk and around the shoulder region for the choice of “non-acupoint” control. Another commonly used strategy has been to arbitrary find a site several millimeters or centimeters away from the verum acupoint. It is also suggested that in order to avoid the risk of ‘contamination’ by another meridian, one may like to select a site midway between two parallel meridians, which would theoretically have minimal influence from either of the two meridians.

4. The challenge of determining a quantifiable stimulation

4.1. From mechanical stimulation to electrical stimulation

According to TCM, the importance of proper and effective manipulation of the needle is no less than that of the selection of the appropriate acupoint. In fact, it may take years to master any kind of manipulation (tonifying or dissipating, warming or cooling) sufficient to “direct the flow of Qi”. Thanks to the introduction of EA, one can readily and precisely set the parameters of the electric pulses in scientific studies.

Among the important parameters of the electric pulses, the frequency seems to be the most critical element. In view of the refractory period of the excitability of the nerve fibers, a cutoff frequency of 100 Hz was set. Regarding the lower end of the frequency, it is usually arbitrarily chosen as 1–4 Hz. Plotting on a logarithmic scale, the mid point between 2 and 100 Hz would be around 15 Hz. Therefore 2-, 15- and 100-Hz are commonly employed as the standard settings for low-, medium- and high-frequency EA, respectively, in clinical and preclinical trials.

4.2. Frequency dependent release of central opioid peptides

The involvement of opioid substances in mediating acupuncture analgesia was first demonstrated by David Mayer in humans [40] and Bruce Pomeranz in mice, when the analgesic effect of acupuncture was prevented or reversed by the opioid receptor blocker naloxone (see [17]). However, opioid peptides include at least three families, the enkephalins, the endorphins and the dynorphins. Does acupuncture activate all three families simultaneously, or can they be activated selectively? Neurochemical studies conducted in humans and rodents revealed that 2 Hz stimulation preferentially increased the CSF content of enkephalins and endorphins, whereas 100 Hz favored the release of dynorphins [19,22]. This has been supported by pharmacological studies using type-specific opioid receptor blockers [6] and cross tolerance studies [7]. Intrathecal injection of antibodies against enkephalin prevented the analgesic effect induced by low-, but not high frequency electrical stimulation. In contrast, intrathecal injection of antibodies against dynorphin prevented high- but not low frequency EA-induced analgesia [18]. As an extension of these experimental approaches, a dense-and-disperse (DD) mode of stimulation was designed, where 2 Hz was automatically alternating with 100 Hz, each lasting for 3 s, which, as expected, evoked the release of both enkephalins and dynorphins, resulting in a synergistic interaction [8,20]. The findings obtained in the rat experiment have been verified in clinical studies. Hamza et al. [15] examined the frequency-sensitive effect of transcutaneous electrical nerve stimulation (TENS) on the postoperative opioid analgesic requirement (using patient controlled administration device, PCA) in 100 women undergoing major gynecological procedures with a standardized general anesthetic technique. Patients were assigned to four groups: sham, 2-Hz, 100-Hz, and the 2/100-Hz alternating (dense-and-disperse, DD) mode. The DD group showed a decrease in morphine consumption by 53% compared with the sham group; while 2- and 100-Hz groups only showed 32% and 35% reduction, respectively. All three “active” TENS groups reduced the duration of PCA therapy, as well as the incidence of nausea, dizziness and itching. Similar experiments with single-blind randomized controlled design were performed by Tong et al. [58] in normal volunteers, using the mechanical pain thresholds (MPTs) and heat pain thresholds (HPTs) as outcome measures. The results showed that HPT increased significantly only in the DD group, whereas MPT increased significantly in both DD and 100 Hz group. However, Law and Cheing [32] did not find the advantage for the DD mode.

There is evidence showing that the therapeutic effect induced by 2 and 100 Hz stimulation may work through different mechanisms. It is interesting to assess whether the differences between 2 and 100 Hz electrical stimulation are qualitative or quantitative. Sluka et al. [51] reported that in rats with joint inflammation, increased release of serotonin in the spinal cord occurred during low, but not high frequency stimulation. On the other hand, high-frequency, but not low-frequency stimulation reduces aspartate and glutamate release in the spinal cord dorsal horn [52]. In rats made tolerant to morphine, 2 Hz was no longer effective [50]. If the two modes of stimulation indeed work through different mechanisms, they should not produce cross tolerance with each other, a hypothesis that was experimentally tested. Results showed that prolonged stimulation with 2 Hz EA resulted in a gradual diminution of the analgesic effect, labeled as tolerance. Rats made tolerant to 2 Hz EA were fully responsive to 100 Hz, and vice versa, suggesting that they may be mediated by different receptors. Indeed, the rats that were made tolerant to the DD mode of stimulation showed no analgesic responses to either 2 or 100 Hz stimulation [7].

Of added interest is that the efficacy of 2- versus 100-Hz EA seems to be disease-dependent. Zhang et al. [71] reported that in a rat inflammatory model, 10 Hz EA, but not 100 Hz EA suppressed inflammation by activating the hypothalamus–pituitary–adrenal axis (HPA) and the related circuits. In a rat spinal nerve constriction neuropathic pain model, Sun et al. [56] revealed that the 2 Hz EA stimulation for 30 min suppressed cold hypersensitivity for more than 24 h, whereas 100 Hz was without effect. This was accounted for by the long term depression in the spinal dorsal horn induced by the 2 Hz EA [67]. It is noteworthy that the sharp difference in therapeutic effects between 2 and 100 Hz was also found in treat-

ing other disorders in addition to pain. Kim et al. [29] used the motor evoked potentials to analyze the effect of low versus high frequency electrical acupoint stimulation on the recovery of motor function after ischemic stroke. They found that 2 Hz was much more effective than 120 Hz in all parameters surveyed, including the latency, central motor conduction time and amplitude of motor evoked potentials. Zhou et al. [74] studied the brain stem mechanisms underlying acupuncture modulation of cardiovascular responses in rats. They found that 2 Hz was much better than 100 Hz, even significantly better than 10 Hz.

However, in contrast to the majority of reports showing therapeutic effects in favor of low frequency, there are examples indicating that 100 Hz is better than 2 Hz, at least in relieving muscle spasm induced by spinal trauma [11,60].

The central pathways mediating low and high frequency EA analgesia were explored by Han and Wang [21]. Signals from 2 Hz EA seem to sequentially activate the arcuate nucleus of the hypothalamus (β-endorphinergic neurons), PAG, medulla (enkephalinergic neurons), and the dorsal horn to suppress nociceptive transmission, 100 Hz EA activated a short parabrachial nucleus-PAG-medulla-spinal dorsal horn pathway involving dynorphin. Xue et al. [69] reported that 100 Hz EA for 30 min produced a 10-fold increase in the dynorphin content in the dorsal horn, but not in the ventral horn.

Thus, the accumulating evidence suggests that 2 and 100 Hz EA can be regarded as two distinct therapeutic entities.

4.3. The role of intensity of stimulation

Compared to the frequency, the intensity of EA has not been given enough attention. One of the reasons is that there is not much room for a sizeable change. Unlike the frequency which appears to have a 50- to 100-fold range (from 1–2 to 100 Hz), the range for intensity change between the sensory threshold and the pain threshold may not exceed 6-fold (0.5–3 mA, applied to needles inserted into the skin).

The intensity of EA stimulation necessary to cause an analgesic effect seems to very according to the physiological status of the subject. Barlas et al. [3] reported that in healthy human volunteers without pre-existing pain, EA with a higher intensity is needed to elevate the pain threshold. Wang et al. [63] compared two intensities of electrical stimulation for controlling post-operative pain, using the level of patient-controlled analgesia (PCA) as outcome measurement. Results showed that threshold level (4–5 mA) TENS reduced the analgesic requirement by 34%, whereas doubling threshold intensity (9–12 mA, strong but not painful) can reduce the PCA requirement by 65%. Under inflammatory conditions, however, a much lower intensity appears to be preferable. Liu et al. [37] used EA for the treatment of complete Freund's adjuvant (CFA)-induced monoarthritis in rat. Among the three levels of intensity tested (1–2, 1–3, 2–4 mA), the lowest intensity was most effective to reduce pain scores, followed by medium intensity. Similar results were obtained by Lee et al. using an inflammation model involving carrageenan-induced paw inflammation in rats [34]. Only weak stimulation produced therapeutic effect of reducing pain and swelling, accompanied by a reduction of PGE2 synthesis.

4.4. How long and how often should acupuncture be delivered?

With regard to the optimal duration for an EA session, we reported in our original study on humans that a period of 30 min is required for the full expression of analgesic effect in normal volunteers, which fits quite well with the clinical experience of tens of thousands of surgical operations under "acupuncture anesthesia" in the 1970s in China. Cheing et al. tested the effect of EA lasting 20, 40 and 60 min for the treatment of osteoarthritic pain, and found that EA for 40 min achieved the strongest and longest lasting therapeutic effect [5].

It should be pointed out that continuous acupuncture stimulation for more than 1–2 h may lead to a diminution of analgesic effect, a phenomenon known as "acupuncture tolerance". One of the underlying mechanisms is the accelerated release of central cholecystokinin octapeptide which acts against the analgesic effect of the endogenous opioid peptides [23,24]. Therefore, excessive duration of acupuncture stimulation is not recommended.

Liu et al. [37] further tested the optimal paradigm needed for EA treatment in the rat model of CFA-induced monoarthritis. Among three treatment regimens (once, twice and five times a week), once a week was most effective, followed by twice a week. Five times a week schedule was of no therapeutic effect in that specific case.

5. How reliable and reproducible are the therapeutic effects of acupuncture for acute and chronic pain?

5.1. Acute pain: post-operative analgesia

Post-operative pain is one of the typical acute pains observed in clinical practice. Exacerbation of acute pain can lead to neural sensitization both peripherally and centrally. In contrast, good pain control after surgery is important to prevent negative outcomes such as tachycardia, decrease in alveolar ventilation, and poor wound healing. A systematic review [55] quantitatively evaluated the efficacy of ARTs as adjunct analgesics for post-operative pain management. They searched the databases in the period of 1966–2007, and 15 RCTs were found. Weighted mean difference for cumulative opioid analgesic consumption was −3.14, −8.33, and −9.14 mg at 8, 24, and 72 h, respectively. Post-operative pain intensity (visual analogue scale) was also significantly decreased in the acupuncture group at 8 and 72 h compared with the control group. Unterrainer et al. recently reported the effect of pre- and post-operative TENS on post-operative opioid requirement after major spinal surgery (lumbar spinal fusion) [59]. Electrical stimulation at 100 Hz was administered for 30 min before skin incision, 8 h after skin closure, and additional 30 min on the first post-operative day. Post-operative analgesic demand was significantly reduced compared to the control group. The analgesic sparing effect was significantly weakened if the pre-operative 30 min preemptive TENS was omitted. Sim et al. [49] showed that pre-operative EA reduces intraoperative alfentanil consumption, and a morphine sparing effect during the early post-operative period. Lin et al. [36] also found pre-operative EA reduced post-operative analgesic requirements and associated side effects in patients undergoing lower abdominal surgery. In contrast, White [64] underlined the importance of post-operative stimulation in a setting in which the post-operative stimulation lasted for 72 h, while pre-operative stimulation was only 30 min. Interestingly, intraoperative EA during the period of anesthesia seems to have no effect on post-operative nausea and analgesic requirement [12].

Taken together, most reports seem to recognize that perioperative ART is useful to decrease post-operative pain and nausea/vomiting [9]. Since ARTs are cost effective for controlling post-operative pain and nausea/vomiting and lack of clinical toxicity, clinicians have been called onto incorporate these "acustimulation" techniques routinely on to their perioperative therapeutic armamentarium [65].

5.2. Chronic pain

Compared to the clear efficacy of acupuncture on acute (e.g., post-operative) pain, the effectiveness of acupuncture on the treatment of chronic pain seems less straightforward. Wang et al. [62] concluded from the peer-reviewed literature that acupuncture and

other forms of acustimulation are effective only in the short-term management of low back pain, neck pain, and osteoarthritis pain involving the knee. Nnoaham and Kumbang [44] carried out a systematic review of acupuncture and related techniques for chronic pain (pain lasting for more than 3 months). They selected 25 high quality RCTs (involving 1281 patients) from a total of 124. Out of 22 studies using inactive stimulation as controls, 13 showed a favorable outcome for the active treatment. Out of 15 multiple treatment studies, eight were favorable to active treatment. The following are the responses of some prevalent chronic pain conditions to ARTs.

Chronic low back pain is a highly prevalent chronic pain condition. In a review of acupuncture treatment for this condition, Khadilkar et al. [28] identified four high-quality RCTs (585 patients). They found conflicting results from two different studies regarding generic health status, with one study showing no improvement on the modified Sickness Impact Profile and another study showing significant improvements on several, but not all subsections of the SF-36 questionnaire. The common picture is that while the acupuncture group is significantly superior to the wait-list group, it may or may not be more potent than the placebo group. This raised the question whether the acupuncture effect is due to conditioning and expectation, rather than the physiological effect produced by the acupuncture *per se*.

Chronic shoulder pain seems to show a better response to acupuncture. In a recent German randomized clinical trial chronic shoulder pain patients were treated by Chinese traditional acupuncture in an outpatient care environment [43]. Fifteen treatments were given over 6 weeks. A 50% reduction of pain measured by VAS 3 months after the end of treatment was taken as the primary outcome for responders. The percentages of responders were 65% for verum acupuncture, 24% for sham acupuncture and 37% for untreated control. Descriptive statistics showed greater improvement of both pain scores and shoulder mobility for the verum group versus the sham group ($P < 0.01$) and the verum group versus the control group ($P < 0.01$).

Osteoarthritis is the most common form of joint disease. It is the leading cause of pain and physical disability in the elderly. Rutjes et al. [46] conducted a comprehensive review of 18 small trials of TENS among 813 patients. Overall the active TENS group showed a mild analgesic effect. The authors concluded that the mean difference in pain scores between electrostimulation and the inactive control was approximately only 0.2 cm on a 10 cm visual analogue scale which is too small to be considered clinically meaningful.

Among the studies reviewed, two articles published in the Annals of Internal Medicine using acupuncture for the treatment of osteoarthritis of the knee joint are of particular interest since they reported opposite results. The RCT of Berman et al. [4] observed positive results while that of Scharf et al. [47] did not. Detailed comparisons reveal some clues to resolve the discrepancy. First, the effect of acupuncture seemed to be strengthened by performing more treatment sessions. Berman et al. used 23 sessions, while Scharf et al. used only 10. Second, Berman et al. used two needles in the non-acupoints group, while Scharf et al. used 10. It was reported that stimulation of the "non-acupoint" can also produce some analgesic effect, albeit weaker in efficacy [35]. Finally, Berman et al., but not Scharf et al., used EA to supplement manual needling which may strengthen the therapeutic effect.

A recent study of Ahsin et al. [2] also showed that EA was effective for the treatment of chronic osteoarthritis. In their study the verum EA group was given 20–25 min EA per session, once a day for 10 days, and the control group was given sham needle insertion at non-points without electrical stimulation. The verum EA group showed significant improvements in pain, stiffness and disability, accompanied by a significant increase in plasma β-endorphin ($p = .001$) and a significant fall in plasma stress hormone cortisol ($p = .016$). In fact there are studies showing that leaving the needle in situ without movement or electrical stimulation does not produce analgesic effects [15]. Collectively it may be rational to try EA rather than using only manual needling in major clinical trials.

Spinal trauma is a condition frequently occurring after car accidents and falls. Severe spinal cord injury often induces flaccid muscle paralysis which may turn into spastic paralysis accompanied by cramping pain, and is hard to treat. Wang et al. [60] used transcutaneous electrical acupoint stimulation (TEAS) to treat spastic pain. They found that only 100 Hz, but not 2 Hz stimulation suppressed the muscle spasticity. Of note, in this unique case, 2 Hz EA can be regarded as the control for the 100 Hz EA, since the psychological effect was the same in both groups. 100 Hz EA was shown to release dynorphin in the spinal cord [19]. Consistently, intrathecal injection of the kappa opioid agonist U-50488 produced a similar spasmolytic effect [11].

Fibromyalgia (FM) affects 2% of the population with a 7:1 female:male prevalence, and no cure is seemingly known. Acupuncture has been tried, although results are inconclusive. Four systematic reviews published in 2007–2009 showed pessimistic results, ranging from "no" to "mixed" or "moderate" effect. However, there are several papers showing more optimistic results. Harris et al. [25] at the University of Michigan examined FM symptom severity as well as the availability of μ opioid receptors in the brain, assessed by positron emission tomography (PET) using ^{11}C labeled carfentanyl as the tracer. A negative correlation was revealed between symptom severity and the availability of μ opioid receptors, especially in brain regions known to play a role in pain modulation, such as the nucleus accumbens, the amygdala and the dorsal cingulate gyrus. This result suggests that the effect of acupuncture depends not only on the brain's ability to release opioid peptides, but also on the availability of μ opioid receptors in specific areas of the brain.

6. Challenges in designing a control group for clinical trials of acupuncture

In all clinical interventions, the pharmacological, physiological and even surgical effects are always accompanied by a psychological effect. Indeed, in clinical practice, there is no need to avoid the psychological component. However, for research purposes, it is mandatory to design a control so that the therapeutic effect from a given intervention can be distinguished from psychological effects. In acupuncture research there is a justifiable concern that the placebo effect may constitute the major part, if not the whole of the acupuncture effect. To solve this problem, a control manipulation designed as close as possible to the verum acupuncture is indispensable.

6.1. Skin touching to mimic the manual acupuncture

The Streitberger needle is a blunted, telescopic device that simulates acupuncture but does not penetrate the skin [54]. This ingenious device has reportedly been validated for use in acupuncture studies. However, concerns have been raised from two important perspectives. One is that skin touch is not an inert stimulation. From my own experience of being a volunteer for the inventor of the needle, the sensation produced by the needle tip "touch" was substantial. It may activate some cutaneous C fibers [39]. On the other hand, for those who had experienced acupuncture *deqi* sensation before, the unique deqi feeling can hardly be mimicked by skin touching. It is for this reason that subjects who had previously experienced *deqi*, are often excluded from clinical trials.

6.2. Minimal electrical stimulation to mimic the electroacupuncture

To mimic the verum EA, one can use the "minimal stimulation" strategy by reducing the current intensity to a threshold level, so that the subject can still feel the characteristic electrical pulses,

albeit weak in intensity. Aside from the reduction of intensity, one can also reduce the stimulation time by using intermittent current, such that the current is delivered 1-min on and 2-min off, so the subject can feel the electric impulses wax and wane. In a study using TEAS for stopping the urge to smoking, both 5 mA (threshold stimulation) and 10 mA (double threshold) groups were effective in reducing the smoking urges. But when the stimulation was shifted to intermittent 5 mA, the smoking urge suppressive effect disappeared [31]. This may serve as a new type of minimal stimulation control for both EA and TEAS.

6.3. How to measure the subjective and objective changes induced by acupuncture

It is well known that expectation coexists with the physiological effect of acupuncture, and it is very difficult to distinguish the two factors. Kong et al. [30] designed a sophisticated experiment using both behavior and fMRI approaches. They found that conditioning positive expectation can amplify acupuncture analgesia as detected by subjective pain sensory rating changes and objective fMRI signal changes in response to calibrated noxious stimuli. They revealed that expectation-induced analgesic effect can occur at designated body sites. They also found that sham acupuncture and verum acupuncture may produce similar degree of analgesic effect, yet the verum acupuncture did induce more prominent fMRI changes in certain brain areas compared to that induced by sham stimulation. Brain substrates involved in this process include bilateral rostral anterior cingulate cortex/medial prefrontal cortex, left orbital prefrontal cortex and dorsolateral prefrontal cortex. They suggest that expectation may activate some forebrain structures to induce an up–down influence on subcortical brain matrix for modulation of pain perception, whereas acupuncture may induce a peripheral–central effect to suppress pain perception mechanisms. This seems to fit with the findings of Harris et al. [25] that although both verum and sham acupuncture produced identical levels of pain relief in FM patients, the brain pathways mediating these two effects appear very distinct.

7. Conclusions

7.1. Areas of consensuse

(a) Acupuncture, electroacupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS) can be regarded as a continuum of stimulation techniques, that can be collectively entitled "acupuncture-related technique (ART)". In the present study, this proposed term also includes transcutaneous electrical nerve stimulation (TENS).
(b) Clinical and scientific interest in ART has been increasing dramatically in the recent decade, compared to the last three decades in the previous century, as shown by the steep increase of scientific basic and clinical publications related to acupuncture [16].
(c) Pain management has been the most thoroughly studied and best documented condition for treatment with ART.
(d) For the control of acute surgically-induced pain, preoperative and post-operative administrations of ART can ameliorate post-operative pain and nausea/vomiting.
(e) In most chronic pain conditions, ART reduces pain as compared to untreated or wait-list controls.
(f) Multiple sessions of ART (1–2 times per week for several weeks) are necessary for the treatment of chronic pain conditions in order to obtain a cumulative effect.
(g) For sensitive individuals and in hypersensitive disease status, weaker and sparser ART treatments may produce better therapeutic effects, compared to stronger and more frequent treatments.
(h) Central opioid receptors of various types are important in mediating the analgesic effect induced by ART of different frequencies.
(i) Psychological components such as conditioning and expectation may play important roles in ART-induced analgesia.
(j) Frequency-specific characteristics of ART-induced analgesia suggest a physiological component independent of psychological factor, since the patient is not in a position to characterize which frequency would produce a better therapeutic effect.
(k) Acupuncture has both local and distant analgesic effects that may be mediated by different mechanisms.
(l) Additional clinical and basic studies are needed to better define optimal conditions of ART in order to maximize the physiological component for cost effective pain management (Fig. 1).

7.2. Areas of controversy

(a) The meridians have a unique structural basis independent of the nervous system.
(b) Acupoint selection should be tailored to the individual patient to achieve the best therapeutic effect compared to predetermined, standardized acupoint prescriptions for a given disease entity.
(c) Inserting a needle anywhere in the body can produce the same therapeutic effect.
(d) The majority of acupuncture effects can be accounted for by placebo effects, an understanding which may lead to the neglect of further optimization of the mode and precise parameters of the stimulation.
(e) EA or TEAS should be used more often in future acupuncture-related clinical trials.
(f) TEAS should be used preoperatively in most surgical procedures for cost effective reduction of post-operative pain and nausea/vomiting.

Conflict of Interest

There is no conflict of interest for the authors.

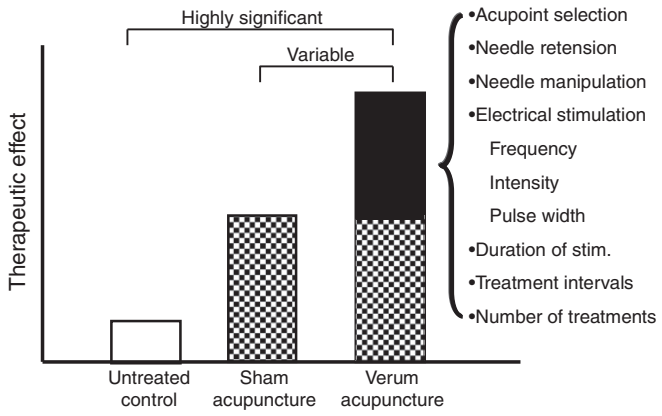

Fig. 1. Diagram showing that the therapeutic effect of acupuncture is composed of two parts, the psychological effect (shaded area) and the physiological effect (filled area). The latter is again determined by an array of factors. Optimization of these factors is likely to maximize the physiological effect, making the difference between the sham and the verum group significant.

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