Review Article

Acupuncture Analgesia: I. The Scientific Basis

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Acupuncture has been used in China and other Asian countries for the past 3000 yr. Recently, this technique has been gaining increased popularity among physicians and patients in the United States. Even though acupuncture-induced analgesia is being used in many pain management programs in the United States, the mechanism of action remains unclear. Studies suggest that acupuncture and related techniques trigger a sequence of events that include the release of neurotransmitters, endogenous opioid-like substances, and activation of *c-fos* within the central nervous system. Recent developments in central nervous system imaging techniques allow scientists to better evaluate the chain of events that occur after acupuncture-induced stimulation. In this review article we examine current biophysiological and imaging studies that explore the mechanisms of acupuncture analgesia.

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Acupuncture is an important part of health care in Asian culture that can be traced back almost 3000 yr. This ancient Chinese intervention consists of applying pressure, needling, heat, and electrical stimulation to specific acupuncture points to restore patients to good health.[1,2] The practice of acupuncture in the United States was largely limited to Asian ethnic groups until about 30 yr ago. President Richard Nixon's visit to China in 1972 was the seminal event opening the door to Chinese medical practices. Since that time, there has been a growing interest in integrating acupuncture into Western medical practice.[3] In 1992, Congress established the Office of Alternative Medicine. Based upon the results of well-designed and appropriately controlled clinical trials, the National Institutes of Health (NIH), in November 1997, issued a statement that supported the efficacy of acupuncture for specific conditions, such as pain, nausea, and vomiting.[4] In 1998, acupuncture became the most popular complementary and alternative medicine modality prescribed by Western physicians.[5] In 1999 the National Center for Complementary and Alternative Medicine was established within the NIH.

Despite the widespread use of acupuncture for pain management, the mechanism of acupuncture-induced analgesia remains unclear. The objective of this review article is to critically evaluate available peer-reviewed scientific literature, examining the neurophysiologic mechanisms and clinical efficacy of acupuncture analgesia. The aim of this article is not to translate the Eastern theory of acupuncture into a Western conceptual framework, but rather to provide a scientific interpretation of acupuncture analgesia and related forms of acupuncture based on peer-reviewed basic science and clinical research. We will focus on recent developments, including imaging studies, to complement other recent reviews of the biological basis of acupuncture and its electrical equivalent (electroacupuncture; EA).[6,7]

TRADITIONAL ACUPUNCTURE THEORY

Traditional Chinese acupuncture is a philosophy that focuses more on prevention than treatment of illnesses. The Chinese medical acupuncture philosophy presumes that there are two opposing and complementary forces that coexist in nature: Yin and Yang. These two forces interact to regulate the flow of "vital energy," known as Qi. When a person is in "good health," Yin and Yang are in balance, and the flow of Qi is smooth and regular. When Yin and Yang become "unbalanced," there are disturbances in Qi, which lead to illness and disease. The ancient Chinese believed that Qi flows through a network of channels called meridians, which bring

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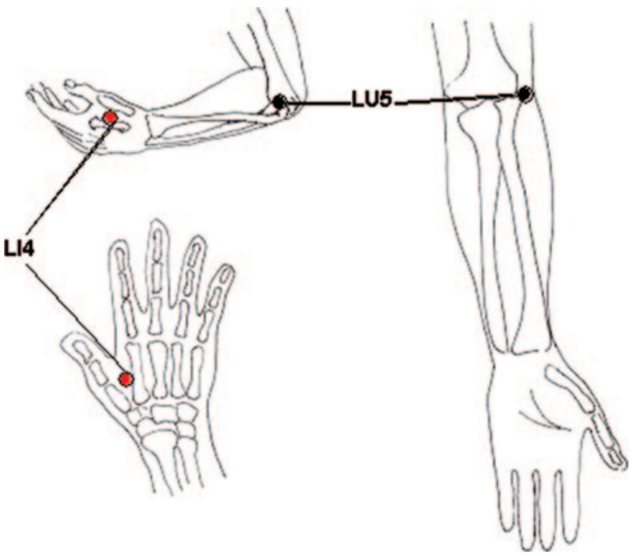

Figure 1. The locations of acupuncture points: large intestine 4 (LI4) and lung 5 (Lu 5).

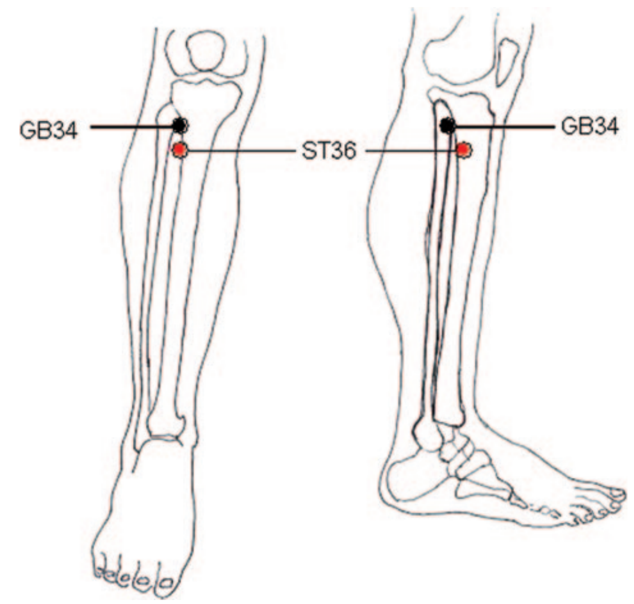

Figure 2. The locations of acupuncture points: gallbladder 34 (GB34) and stomach 36 (ST36).

Qi from the internal organs to the skin surface. Along these meridians there are acupuncture points that can be stimulated to correct the imbalance and restore the body to normal health.[1]

MODERN ACUPUNCTURE THEORY

The traditional Chinese perspective is not based on anatomical, physiological, or biochemical evidence, and thus cannot form the basis of a mechanistic understanding of acupuncture. Western theories are primarily based on the presumption that acupuncture induces signals in afferent nerves that modulate spinal signal transmission and pain perception in the brain.

In 1987, Pomeranz proposed that acupuncture stimulation activates A-δ and C afferent fibers in muscle, causing signals to be transmitted to the spinal cord, which then results in a local release of dynorphin and enkephalins. These afferent pathways propagate to the midbrain, triggering a sequence of excitatory and inhibitory mediators in the spinal cord. The resultant release of neurotransmitters, such as serotonin, dopamine, and norepinephrine onto the spinal cord leads to pre and postsynaptic inhibition and suppression of the pain transmission. When these signals reach the hypothalamus and pituitary, they trigger the release of adrenocorticotropic hormones (ACTH) and endorphins. Pomeranz's theory was confirmed by a large series of experiments by his research laboratory and other investigators.[8–17] This conceptual framework for acupuncture-induced analgesia has also been investigated in a series of neurophysiologic and imaging studies over the last three decades.

Neurophysiological Studies

Volunteer Data

One of the first volunteer studies that examined the scientific basis of acupuncture analgesia was published in 1973 by a group of investigators who used a model of acute pain mediated by potassium iontophoresis with gradual increases of electrical current.[9] The volunteers were randomized to receive acupuncture at large intestine 4 (LI4) (Fig. 1) and stomach 36 (ST36) (Fig. 2) or IM morphine. The investigators found that both acupuncture and morphine increased the subjects' pain threshold by an average of 80%–90%. The acupuncture-induced increase in the pain threshold was gradual, with a peak effect at 20–40 min, followed by an exponential decay with a half-life of approximately 16 min, *despite* continued acupuncture stimulation.[9] Importantly, when the researchers injected local anesthetic into these acupuncture points before the stimulation, the acupuncture became ineffective in increasing the pain threshold (Fig. 3). This suggested that an intact sensory nervous system is essential for the transmission of acupuncture signals. The investigators also found that the analgesic effect was the same regardless of which side of the body was stimulated. Finally, a greater cumulative effect was observed when multiple acupuncture points were stimulated simultaneously.

In a follow-up study, Lim et al.[10] found that direct stimulation of peripheral nerve sensory fibers increased the pain threshold in a manner similar to that caused by standard acupuncture technique. These findings are remarkably consistent with the findings from a more recent clinical study involving the use of transcutaneous electrical stimulation for minimizing postoperative pain.[18]

Experimental Data

The difficulty in developing suitable animal models has been one of the major obstacles in the experimental study of the mechanism of acupuncture anesthesia.[11] Professor Han and his colleagues at Peking

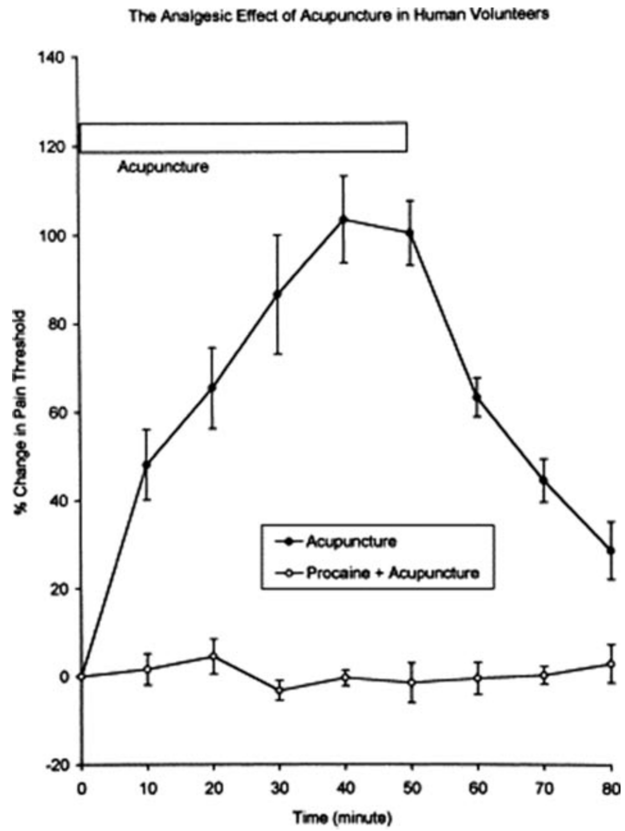

Figure 3. The analgesic effect of acupuncture in healthy volunteers. Reproduced with permission from Ulett GA, Han S, Han JS. Biol Psychiatry, 1998, 44, 129–38, ©Elsevier.

University performed multiple trials using various animal models in search of the ideal experimental model for acupuncture research[1]. The investigators initially used a rabbit model, but later adopted a rat model because rats are commonly used in pain research and are easier to handle.

In 1973, Professor Han and his colleagues applied acupuncture stimulation to a rabbit for 30 min to achieve an analgesic effect. The cerebrospinal fluid (CSF) was then removed and infused into the lateral ventricle of an acupuncture-naive recipient rabbit. This resulted in an increase in the pain threshold in the recipient rabbit. The investigators concluded that acupuncture-induced analgesia was associated with the release of neuromodulatory substances into the CSF. The investigators also noted that there was no increase in analgesic response when saline or CSF from nonacupuncture control was infused into an acupuncture-naive recipient rabbit.[11]

In 1976, Pomeranz and Chiu[8], using a mouse model, found that administration of the opioid antagonist-naloxone blocked the acupuncture-induced analgesic activity. Similarly, in a human model, Sjolund and Ericksson, as well as Mayer[19,20], were able to demonstrate increased levels of endorphins in CSF after EA stimulation, *and* the reversal of acupuncture analgesia by naloxone. This again suggested the involvement of endorphins in human acupuncture analgesia. Several subsequent studies supported the hypothesis that acupuncture triggers the release of endorphins and other endogenous opioids within the central nervous system (CNS), and this appears to be responsible for the analgesic properties of acupuncture.[12,21–23] Recent EA studies also indicate that low-frequency EA induces the release of enkephalin and β-endorphin, whereas high-frequency EA induces the release of dynorphin.[24]

The development of tolerance to EA analgesia was first described in 1979 after the observation that the duration of the acupuncture analgesic effect was not directly correlated to the duration of acupuncture administration.[25] In a follow-up study, this research group described that EA applied to a rat model for a 30-min period increased the pain threshold by 89%.[26] When the EA stimulation was repeated over six consecutive sessions with 30 min between each session, however, the resulting analgesic effect diminished progressively and eventually returned to a baseline level.[26] This tolerance to acupuncture analgesia is thought to be the result of desensitization or "down regulation" of CNS opioid receptors, as well as the release of antiopioids such as cholecystokinin octapeptide.[27] Subsequently, Han et al.[28] were able to reverse acupuncture tolerance by an intraventricular injection of cholecystokinin antiserum in a group of rats which received continuous 6-h EA stimulation.

Guo et al.[29,30] investigated whether high-frequency EA differs from low-frequency EA in gene expression using *c-fos* as a marker of activation in various parts of the rat brain. These investigators found that low-frequency EA resulted in much higher *c-fos* expression in the arcuate nucleus when compared with that after high-frequency stimulation, and when compared with that after simple needle insertion into an acupoint without electrical stimulation in a control group. *In situ* hybridization studies revealed that low-frequency stimulation increased the expression of messenger RNA for the enkephalin precursor protein, whereas high-frequency stimulation increased the expression of mRNA for the dynorphin precursor protein. Thus, there appear to be differential effects of low versus high-frequency EA stimulation on *c-fos* expression, as well as on the transcription of mRNA by various opioid genes in the brain. However, *c-fos* expression can also be caused by nonspecific stimulations (e.g., immobilization or handling of the animal). Furthermore, mRNA levels may not correlate with actual peptide levels. It is important to note that while these studies suggest EA analgesia is at least partly mediated through endogenous opioids, further work is required. For example, it is possible that acupuncture needles simply function as electrodes, and that the endogenous opioid production is a result of electrostimulation with no relationship to acupuncture.

[1]Direct communication with Professor Han, January 2007.

Pan et al.[31–33] studied whether there is an overlap of central pathways between noxious stimulation and acupuncture stimulation in rats. These investigators found that noxious stimulation (caused by immersing the footpad into 52°C water) and EA (4 Hz) both induced *c-fos* expression in the anterior lobe of the pituitary gland and in the arcuate nucleus as well as in nearby hypothalamic nuclei. These researchers also found similar *c-fos* expression in the anterior lobe of the pituitary gland in response to immobilization stress in awake rats. It seems that, although the anterior pituitary cells that respond to stress are activated by both acupuncture and pain stimulation, the mechanism of pituitary cell activation seems distinct from the activation occurring in stress because different hypothalamus nuclei are involved.[31] A follow-up study by the same research team was conducted to identify the function of these activated pituitary cells.[32] The investigators found that *fos*-immunoreactive cells activated by noxious stimulation or EA, co-localized with adrenocorticotropic hormone or thyroid-stimulating hormone, and that noxious stimulation and EA were associated with a similar rise in plasma adrenocorticotropic hormone and β-endorphin. At the hypothalamic level, *c-fos* expression was increased in the mediobasal nuclei (mainly arcuate nucleus and adjacent nuclei) and in the paraventricular nucleus after EA stimulation, but not after noxious stimulation. These data suggested that both somatosensory noxious input and EA activate the hypothalamic-pituitary-adrenocortical axis analogous to stress, but with a specific activation of the mediobasal hypothalamic nuclei, and no activation of intermediate lobe.

Pan et al.[33] confirmed that intact nociceptive primary afferent input is needed to transmit both EA and noxious stimulation signals to the CNS. These investigators found that neither noxious stimulation nor EA stimulation activated the hypothalamic-pituitary-adrenocortical axis or increased plasma ACTH in rats after sensory deafferentation by subcutaneous capsaicin injection to eliminate nociceptive primary afferent input. In contrast, immobilization stress caused a decrease in c-*fos* activation in the hypothalamic pituitary, with no decrease in plasma ACTH.[33] Thus, both noxious stimulation (i.e., pain) and EA activated the hypothalamic-pituitary-adrenocortical axis in a similar fashion. Thus, there appears to be a significant overlap in pain and acupuncture central pathways.

Choi et al.[34] studied the effects of three frequencies of EA (2, 15, and 120 Hz) on chemically induced inflammation of the rat hindpaw. These investigators found that the edema and mechanical sensitivity of rats' hindpaws were strongly inhibited by EA through modulating expression of ionotropic glutamate receptors, particularly *N*-methyl-D-aspartate receptor in the dorsal horn of the spinal cord. Unfortunately, there was no sham-control intervention in this study. Therefore, the phenomena observed may not directly relate to acupuncture alone.

Several conclusions can be made based on the above neurophysiologic studies. First, afferent nociceptive pathways are essential for acupuncture analgesia. Second, acupuncture analgesia is mediated by way of various endogenous neurotransmitters, systemic release of enkephalin and dynorphin, and probably by decreasing the local inflammatory response via *N*-methyl-D-aspartate receptors. Third, the acupuncture-induced increase in pain threshold is gradual, with a peak effect at 20–40 min, followed by an exponential decay with a half-life of approximately 16 min. Fourth, a prolonged period of acupuncture stimulation results in tolerance that is mediated via release of cholecystokinin octapeptide. Lastly, immunocytochemistry studies indicate that both pain and acupuncture activate the hypothalamic-pituitary-adrenocortical axis.

CNS Imaging Studies

Over the last decade, advanced imaging technologies have been introduced, including positron emission tomography (PET), single-proton emission computer tomography (SPECT), and functional magnetic resonance imaging (*f*MRI). These powerful imaging technologies have made it possible to noninvasively visualize the anatomic and functional effects of acupuncture stimulation in the human brain.

PET Studies

Using PET imaging, Alavi et al.[35] observed that a group of patients who suffered from chronic pain also had asymmetry of the thalamus. This thalamic asymmetry disappeared after acupuncture treatment. One should note, however, that the study did not include a sham-control group. As a result, the PET-related changes do not necessarily indicate a cause-effect relationship.

The "De Qi" sensation is frequently described by patients as soreness, numbness, ache, fullness, or warm sensation that is achieved during manipulation of the acupuncture needles.[1,2] This sensation coincides with acupuncturists describing a feeling of the needle being caught as it is twirled (e.g., the "fish took the bait" or "the needle is stuck to a magnet").[36] Wang et al.[37] suggested that type II afferent fibers are responsible for the sensation of numbness, type III afferent fibers are responsible for fullness (heavy, mild aching), and type IV afferent fibers are responsible for soreness. Hsieh et al.[38] used PET images to visualize the effect of De Qi sensation. This study compared acupuncture stimulation at a frequency of 2 Hz that was associated with a De Qi sensation at LI4 (Fig. 1) to the same stimulation at a sham-acupuncture point as well as to superficial insertion of a needle with minimal stimulation at LI4 *and* to a superficial insertion of a needle at a sham-acupuncture point. The investigators found that only acupuncture stimulation at LI4 with De Qi sensation activated the hypothalamus. Thus, the De Qi at an acupuncture point appears to be the conscious perception of the nociceptive input from the acupuncture stimulation. Biella et al.[39] sequentially applied acupuncture and sham acupuncture at bilateral ST36 (Fig. 2) and LU5 (Fig. 1) during a PET scanning sequence and found that acupuncture, but not sham treatment, activated the left anterior cingulum, superior frontal gyrus, bilateral cerebellum, and insula, as well as the right medial and inferior frontal gyri. These are the same areas activated by acute and chronic pain.[40–48] This finding suggests a possible mechanism for acupuncture analgesia.

Pariente et al.[49] suggested that, in addition to the direct analgesic effect of acupuncture, the anticipation and belief of a patient might also affect the level of therapeutic outcome. Using PET image, these investigators reported that both true and sham acupuncture activated the right dorsolateral prefrontal cortex, anterior cingulated cortex, and midbrain. The investigators suggested that these CNS areas are involved in nonspecific factors such as expectation. The investigators also found, however, that only true acupuncture caused a greater activation in insula ipsilateral to the site of stimulation. Based on the above, one can conclude that the insula region of the brain has a specific role in acupuncture analgesia.

SPECT Studies

Newberg et al.[50] used radioisotope hexamethylpropyleneamine oxime to image the brain of patients suffering from chronic pain and healthy volunteers without pain. The investigators found significant asymmetric uptake in the thalamic regions of patients with chronic pain, but not in the healthy control group. After 20–25 min of acupuncture stimulation, another hexamethylpropyleneamine oxime was administered to these patients and a repeated SPECT study showed that the original asymmetry reversed or normalized after acupuncture therapy that coincided with the reduction of pain. This finding is analogous to the findings in PET studies reported by Alavi et al.[35]

fMRI Studies

Manual Acupuncture Stimulation. Wu et al.[51] found that traditional acupuncture stimulation activated the hypothalamus and nucleus accumbens, but deactivated the rostral part of the anterior cingulate cortex, the amygdale formation, and the hippocampal complex. In contrast, minimal acupuncture activated the supplementary motor area and anterior cingulate cortex and frontal as well as parietal operculum. Superficial pricking induced activation at the primary somatosensory cortex, the thalamus, and the anterior cingulate cortex. Hui et al.[52] found that needle manipulation associated with the De Qi sensation deactivated the nucleus accumbens, hypothalamus, amygdale, hippocampus, para hippocampus, ventral tegmental area, anterior cingular gyrus, caudate, putamen, temporal lobe, and insula. In a follow-up *f*MRI study, Hui et al.[53] explored the subjective psychophysical perceptions (mainly, the conscious perception of the nociceptive input from the acupuncture stimulation) in relation to the CNS responses. They found that subjects who experienced De Qi deactivated the frontal pole, ventromedial prefrontal cortex, cingulate cortex, hypothalamus, reticular formation, and the cerebellar vermis. Subjects who experienced pain instead of De Qi sensation activated the anterior cingular gyrus, caudate, putamen, and anterior thalamus. When these subjects experienced both De Qi and pain, the CNS responses were mixed with predominance of activation at the frontal pole, anterior, middle, and posterior cingulate (Fig. 4). Based on the above studies, these investigators suggest that acupuncture and pain may share similar central pathways, but CNS activities triggered by these two stimulations are opposite to each other. Support for this hypothesis is provided by an *f*MRI study that showed that EA stimulation can modify signals generated by experimental cold pain stimulation.[54]

Of note are the reported discrepancies between the findings of Wu et al. and Hui et al. with respect to the effect of acupuncture on the hypothalamus and nucleus accumbens. There are several possible reasons for the discrepancies between the two studies. First, duration of acupuncture stimulation was different between these studies (1 min vs 2 min). Second, the conscious perceptions of nociceptive input from acupuncture stimulation experienced by study subjects might be different between these studies. Finally, there might be differences in methodology of *f*MRI image analysis e.g., correction of motion artifact and threshold setting for noise between these two laboratories.

Ulett et al.[6] suggested in 1998 that the periaqueductal gray (PAG) region in the brainstem is associated with perception and modulation of noxious stimuli and has an important role in acupuncture analgesia. In an effort to explore these issues using *f*MRI technology, Liu et al.[55] applied acupuncture stimulation to healthy volunteers at LI4 and observed that PAG activity increased with the increasing length of stimulation, with the activated areas ranging from the left ventral to left dorsal lateral to dorsal medial regions. The frequency of activation of PAG after stimulation of the LI4 was calculated by averaging the total number of activations per run (every run consisted four 30-s periods of "acupuncture on"). These investigators also observed that stimulation at a nonacupuncture point resulted in reduction of PAG activity.

EA Stimulation. Wu et al.[56] reported that both true and sham EA stimulation at a common analgesic acupoint, gallbladder 34 (Fig. 2), activated regions of pain central pathways on fMRI.[56] The investigators noted, however, that only true EA stimulation activated the hypothalamus, the primary somatosensory

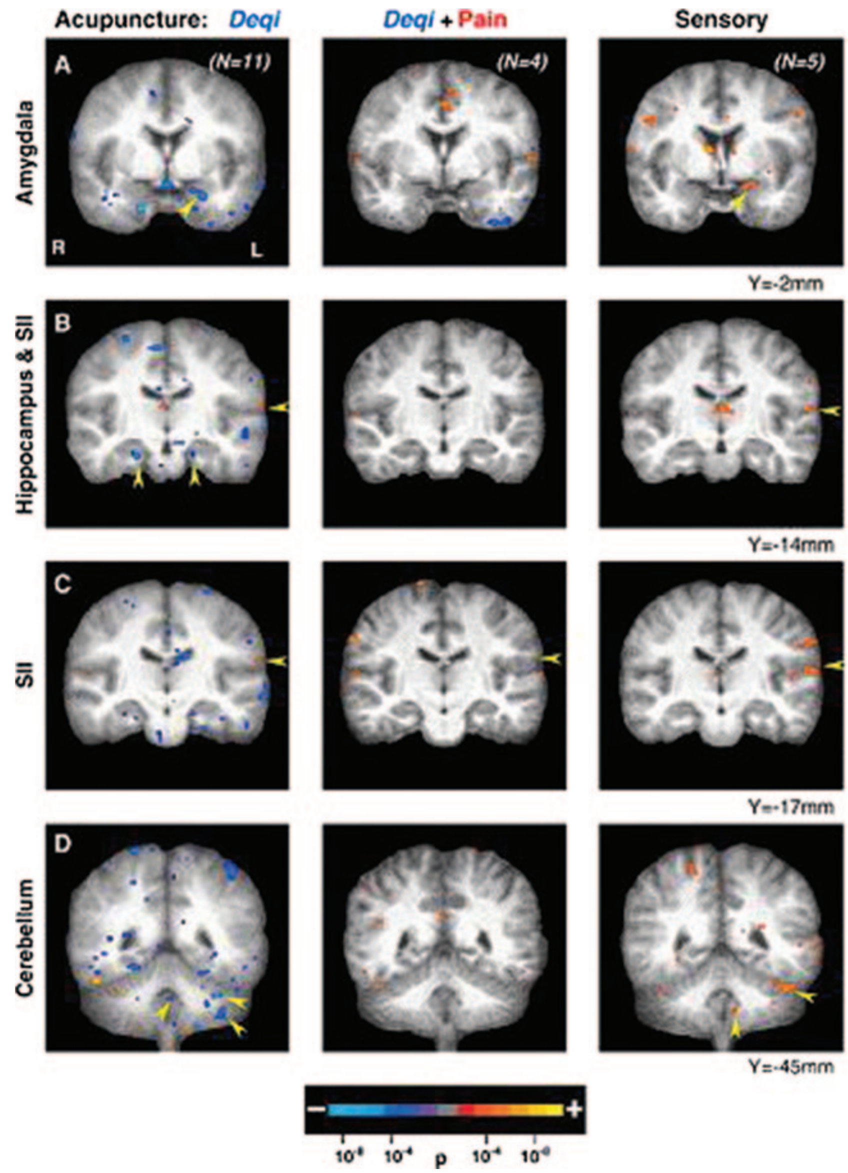

Figure 4. The influence of subjective sensations on fMRI signal changes on major limbic structures, the secondary somatosensory cortex (SII) and the cerebellum during acupuncture at ST 36. Regions of interest are denoted by yellow arrowheads. (Left) Acupuncture with *deqi* sensations (*N* = 11). (Middle) Acupuncture with mixed sensations of *deqi* and sharp pain (*N* = 4). (Right) Sensory control (*N* = 5). (Row A) The amygdala showed signal decrease with acupuncture *deqi*, increase with sensory stimulation and no significant change with acupuncture mixed sensations. (Row B) The hippocampus, bottom arrows, showed signal decrease with acupuncture *deqi*, and no significant change otherwise. (Row C) SII, also shown by the right arrows in Row B, shows signal increase under all three stimulations. Acupuncture, being a form of sensory stimulation, would be expected to result in signal increases in SII, which is in stark contrast to the widespread signal decreases during acupuncture *deqi*. (Row D) With acupuncture *deqi*, the cerebellum showed signal decreases in the vermis and lobules VI and VII. With sensory control, the lateral hemisphere showed signal increases. Reproduced with permission from Hui et al., Neuroimage, 2005, 27, 479–96, ©Academic Press.

cortex and the motor cortex, and *deactivated* the rostral segment of the anterior cingulate cortex. These investigators concluded that the hypothalamus-limbic system was modulated by EA stimulation.

To investigate the direct modulatory effects of EA stimulation in pain responses, Zhang et al.[54] studied a group of healthy volunteers using *f*MRI scanning during experimental cold pain with real or sham EA stimulation. Only the subjects who received EA reported a reduction of pain. The brain images obtained by Zhang et al. showed an acupuncture-induced increased activation in the bilateral somatosensory area, medial prefrontal cortices and Brodmann area (BA32), and a decreased activation in the contralateral primary somatosensory areas BA7 and BA24 (anterior cingulated gyrus). With sham stimulation, there was no observed decrease in pain intensity or *f*MRI image changes. As these areas are frequently involved in pain stimulation, Zhang et al. concluded that EA induces analgesic effects via modulation of both the sensory and emotional aspects of pain processing. This study again demonstrates

Table 1. The Areas of Brain Affected by Acupuncture Stimulation in Imaging Studies

Limbic system
Cigular gyrus[39,50–54,56,57]
Amygadala[51,52,54]
Parahippocampal gryus[51,52]
Hippocampal gyrus[51,52,57]
Insula[38,49,52,53,56,57]
Periaquductal gray[38,55]
Thalamus[35,39,50,54,56,57]
Hypothalamus[38,39,51,56]
Basal ganglia
Putamen[52–54]
Caudate[52,53]
Neucleus accumben[39,51–53]
Cerebellum[38,39,52–54,56]
Brain stem
Substantis nigra[53]
Reticular formation[53]
Pontine nuclei[53]
Dorsal raphe[53]
Somatosenssory II[49,50,52–54,57]

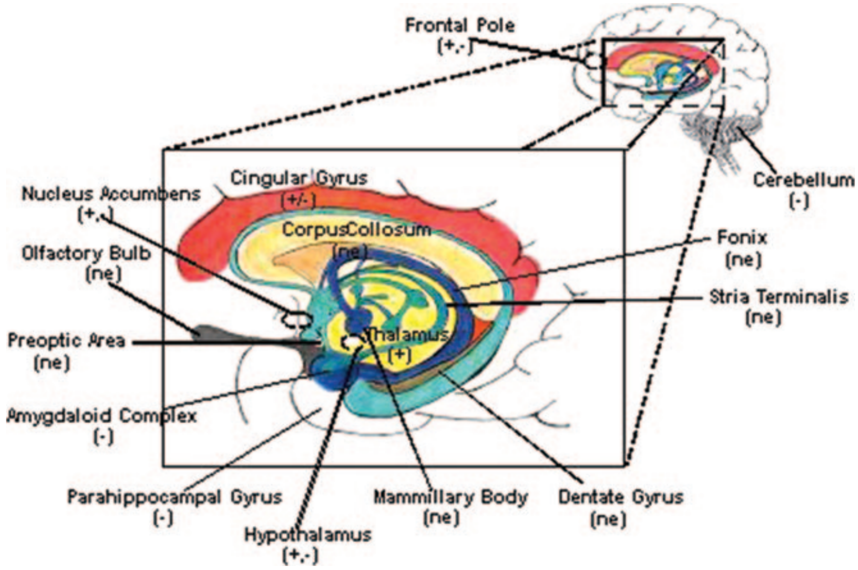

Figure 5. The Limbic System and Adjacent Structures related to acupuncture stimulation. Structures affected by acupuncture stimulations are labeled "+" representing an increase in hemodynamic signals; "−" represents a decrease in hemodynamic signals; "+, −" represents an increased or decreased signal depending on study; "±" represents some regions of this structure that have an increase in signal and some areas that have a decrease in signal, and "ne" represents no effect.

that the hypothalamus-limbic system plays an important role in acupuncture analgesia.

An *f*MRI study by Zhang et al.[57] found that the low-frequency (2 Hz) EA stimulations activated the contralateral primary motor area, supplementary motor area, and ipsilateral superior temporal gyrus, while deactivating the bilateral hippocampus. In contrast, these investigators found that high-frequency (100 Hz) EA stimulations activated the contralateral inferior parietal lobules, ipsilateral anterior cingulate cortex, nucleus accumbens and pons, while deactivating the contralateral amygdala. Therefore, one can conclude that low and high-frequency EA stimulation appear to be mediated by different brain networks. Thus, alternating high/low-frequency EA stimulations may provide the additional analgesia benefit by activating both systems simultaneously.[24,58–62]

Studies Comparing Different Acupuncture Stimulations. Napadow et al.[63] compared manual acupuncture, EA at 2 and 100 Hz, and tactile control stimulation at ST36 in a group of healthy volunteers. They reported that low-frequency EA produced more widespread *f*MRI signal changes than manual acupuncture stimulation. Not surprisingly, both EA and manual acupuncture produced more widespread responses than simple tactile stimulation. These investigators also found that although acupuncture stimulation activated the anterior insula, it deactivated the limbic and paralimbic structures that include the amygdala, anterior hippocampus, cortices of the subgenual and retrocingulate, ventromedial prefrontal cortex, and frontal and temporal lobes.[63] EA at both high and low frequencies produced a significant signal increase in the anterior middle cingulate cortex; however, only low-frequency EA produced activation at the raphe area. Therefore, *f*MRI studies support the hypothesis that the limbic system is central to acupuncture-induced analgesia regardless of the specific modalities.

Several conclusions can be made based on the above CNS imaging studies. First, the hypothalamus may play a central role in acupuncture analgesia. Second, the significant overlap between acupuncture and pain CNS pathways suggests that acupuncture stimulation may affect pain signals processed in the CNS. Third, superficial needling and traditional acupuncture needling activate two different central pathways and yet both provide clinical analgesia.[64–66]

Future studies should on their effects in releasing different opioid-like substances as well as differences in the level of pain relief. The majority of neuroimaging studies in acupuncture are merely explorations of acupuncture signal network. The clinical relevance of data obtained from these studies is unclear. Indeed, participants in a recent conference held by the NIH indicated that standardization of performing and reporting acupuncture neuroimaging results and data sharing between laboratories must be improved.[67]

SUMMARY

Physiological and imaging studies are providing insight into the neurophysiological mechanism of acupuncture analgesia. Recent data suggest that acupuncture triggers a sequence of events involving the release of endogenous opioid-like substances, including enkephalin, β-endorphin, and endomorphin, that modulate pain signals processed along the pathway. Imaging studies demonstrate that the limbic system plays an important role in acupuncture-induced analgesia, as summarized in Table 1 and Figure 5. Future studies will continue to enhance our insight into the mechanism of this ancient analgesic modality.

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Acupuncture Analgesia: II. Clinical Considerations

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BACKGROUND: Acupuncture and related percutaneous neuromodulation therapies can be used to treat patients with both acute and chronic pain. In this review, we critically examined peer-reviewed clinical studies evaluating the analgesic properties of acupuncture modalities.

METHODS: Using Ovid© and published medical databases, we examined prospective, randomized, sham-controlled clinical investigations involving the use of acupuncture and related forms of acustimulation for the management of pain. Case reports, case series, and cohort studies were not included in this analysis.

RESULTS: Peer-reviewed literature suggests that acupuncture and other forms of acustimulation are effective in the short-term management of low back pain, neck pain, and osteoarthritis involving the knee. However, the literature also suggests that short-term treatment with acupuncture does not result in long-term benefits. Data regarding the efficacy of acupuncture for dental pain, colonoscopy pain, and intraoperative analgesia are inconclusive. Studies describing the use of acupuncture during labor suggest that it may be useful during the early stages, but not throughout the entire course of labor. Finally, the effects of acupuncture on postoperative pain are inconclusive and are dependent on the timing of the intervention and the patient's level of consciousness.

CONCLUSIONS: Current data regarding the clinical efficacy of acupuncture and related techniques suggest that the benefits are short-lasting. There remains a need for well designed, sham-controlled clinical trials to evaluate the effect of these modalities on clinically relevant outcome measures such as resumption of daily normal activities when used in the management of acute and chronic pain syndromes.

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Acupuncture and related techniques are nonpharmacologic modalities that are based on classical teachings in Chinese medicine and can be used for the management of pain. Although a National Institute of Health consensus statement published in 1998[1] indicated that acupuncture might be useful for the treatment of certain pain conditions, the recent scientific evidence supporting the use of acupuncture and related forms of acustimulation for the relief of acute and chronic pain has not been critically reviewed. Although many early clinical studies describing the potential clinical usefulness of acupuncture were poorly controlled,[1] more recent studies[2–4] suggest that acupuncture analgesia can be used as an adjuvant in the treatment of conditions such as low back pain (LBP), osteoarthritis (OA) of the knee and neck pain.

In the first review article in this series, we addressed the issue of underlying mechanisms of acupuncture analgesia.[5] In this article, we critically evaluate the clinical evidence regarding the use of acupuncture and its variants in both the short- and long-term management of specific pain syndromes. The focus of this article is on prospectively randomized, sham-controlled clinical trials published in the peer-reviewed medical literature after the consensus panel review of 1998.[1] Anecdotal case reports, case-series, and cohort studies were excluded from this review. We have chosen to focus on sham-controlled trials because of the potential bias for patients and investigators in uncontrolled clinical trials. Indeed, sham-control design is mandatory in acupuncture research to prevent the introduction of reporting bias. This calls for the introduction of an acupuncture-like intervention (e.g., needling to a nonacupuncture point, or a spurious stimulation at established acupuncture points).

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METHODS

We evaluated studies involving clinical analgesic effects of specific forms of acustimulation that include not only traditional Chinese manual acupuncture, acupressure, and electroacupuncture (EA), but also auricular acupuncture and related electrical nerve stimulation techniques such as transcutaneous electrical acupoint stimulation (TEAS), percutaneous electrical nerve stimulation (PENS), percutaneous neuromodulation therapy (PNT), and transcutaneous electrical nerve stimulation (TENS). In reviewing the peer-reviewed literature, all these forms of acustimulation appear to have very similar clinical outcomes. Classic manual acupuncture consists of inserting and manipulating needles into the various acupuncture points whereas acupressure is a technique that uses pressure to stimulate these same acupuncture points. EA is a technique that applies small electrical currents to needles inserted at acupuncture points, whereas TEAS consists of applying an electrical current to cutaneous electrodes that have been placed at acupuncture points. Auricular acupuncture is based on the concept that different ear points represent different organs of the body and includes administration of pressure, needle, or electrical stimulation to specific points on the ear. In contrast, TENS and PENS are based on sending an electrical current either through cutaneous electrode patches (TENS) or acupuncture-like needles to the nerve serving the painful area (PENS). Finally, PNT is a variant of PENS that differs only with respect to the length of needle.

The oldest acustimulation, traditional Chinese manual acupuncture, consists of inserting acupuncture needles into acupuncture points along traditional acupuncture meridians and applying manipulations, e.g., twist, thrust, push and pull until the patient and acupuncturist both experience the "De Qi" sensation. This sensation is frequently described by patients as soreness, numbness, ache, fullness, or warm sensation and by acupuncturists as the feeling of the needle getting caught. Wang et al. suggest that manipulation of the acupuncture needle activates various afferent fibers (type II, III, and IV) and that this activation results in the De Qi sensation.[6] For example, type II afferent fibers (A-β fibers) are responsible for the sensation of numbness/pressure, type III fibers (A-δ fibers) are responsible for a stinging sensation, and type IV fibers (C-fibers) are responsible for a slow diffusion, and aching/nagging sensation. Studies by Langevin et al. indicate that the "needle grasp" sensation experienced by acupuncturists during manipulation is due to the mechanical coupling between the needle and the connective tissue with winding of tissue around the needle during needle rotation.[7,8] In contrast, electrical acupuncture modalities consist of applying different frequencies of electrical stimulation to acupuncture needles inserted at the traditional acupuncture points. Interestingly, a study has shown that 70% of local trigger points correspond to the traditional acupuncture points[9] and that the analgesic effect through electrical acupuncture point stimulation is similar to the electrical stimulation at the corresponding dermatomal levels or peripheral nerve.[10,11] Alternative medical therapies, such as acupuncture and related forms of acustimulation, will likely assume an increasing role in western medicine as scientific evidence supporting these therapies becomes available to practitioners.[12]

In this article, we will discuss evidence supporting the use of acustimulation in chronic LB and neck pain, OA involving the knees, dental pain, surgical and procedure-related pain, acute postoperative pain, and labor pain.

Chronic LBP

Early clinical studies and meta-analysis indicating that acupuncture was not effective for the treatment for chronic LBP[13–15] suffered from methodologic limitations such as inadequate sample sizes, problematic study designs, and the use of invalid outcome measures. In 2001, Carlsson and Sjolund conducted a sham randomized controlled trial (RCT) study among men and women suffering from chronic LBP and found that both manual and EA were superior to sham electrical stimulation in reducing pain and improving sleep patterns, activity repertoire, and analgesic consumption at 4–6 mo postintervention.[16] Interestingly, these positive findings were limited to women subjects. In 2002, Leibing et al. published a RCT involving 131 patients who suffered from LBP and who had normal neurologic examinations for at least 6 mo before their enrollment in the study.[17] These investigators found that an intervention consisting of 26 sessions of combined ear and body manual acupuncture and physical therapy was superior to an intervention that consisted of 26 sessions of standard physical therapy alone for reducing pain, disability, and psychological distress for the first 3 mo of treatment. The beneficial effects of acupuncture were not lasting and at 9 mo after the last intervention there were no differences between the two study groups. A more recent RCT found that the combination of true acupuncture with conservative orthopedic treatment was superior to sham acupuncture combined with conservative orthopedic treatment or conservative orthopedic treatment alone.[18] However, the beneficial effects lasted only 3 mo.

Several studies have also compared the efficacy of alternative electrostimulation techniques (e.g., PENS, PNT) for the treatment of LBP. For example, Ghoname et al.[19] found that PENS was more effective than TENS or exercise therapy in providing short-term pain relief and improved physical function in patients with LBP caused by degenerative disk disease. In a follow-up study, these investigators reported that PENS analgesic effects resulting from alternating electrical stimulation at frequencies of 15 and 30 Hz were superior to analgesic effects resulting from isolated lower (4 Hz) or higher (100 Hz) frequency stimulation.[20] These investigators also studied the effect of the duration of alternating 15 Hz/30 Hz PENS stimulation. They found that analgesic effects resulting from 30 min of stimulation were superior to analgesic effects obtained after 15 min stimulation. However, prolonging the stimulation to 45 min failed to improve the analgesic response. The investigators concluded that there is no additional prolongation of the analgesic effect once the alternated 15 Hz/30 Hz PENS was given for longer than 30 min.[21]

Yokoyama et al.[22] performed a RCT to compare the effects of 8 wk of PENS and TENS therapy for the treatment of long-term pain relief in patients with chronic LBP. They found that, although PENS is more effective than TENS for chronic LBP, the analgesic effect was only sustained for 1 mo posttreatment. The investigators concluded that to sustain the analgesic effect PENS therapy should be continued. Sator-Katzenschlager et al.[23] explored the effectiveness of semi-permanent press needle auricular acupuncture compared with electrical auricular acupuncture as a treatment for LBP. The investigators found that electrical auricular acupuncture is superior to semi-permanent press needle acupuncture in decreasing the severity of LBP and improving psychological well being, activity, and sleep at 3 mo after treatment. Similarly, Meng et al. found that EA is superior to standard therapy such as nonsteroidal antiinflammatory drug, muscle relaxants, paracetamol, and back exercises in elderly patients who suffer from LBP.[24] Since the above long-term acupuncture studies did not have a sham-control group, one can only conclude that there are some differences in the effect of analgesia among various stimulation techniques and treatment modalities.

In conclusion, although data from sham-controlled clinical studies indicate that acupuncture and alternative forms of electrostimulations (PENS and PNT) can serve as a short-term adjunct treatment for LBP management, no study has proven any long-term benefit of acupuncture and/or any other related interventions as a treatment for LBP.[22–26] This lack of long-term benefit may be related to quick degradation of acupuncture-induced endogenous endorphins.[5] Future studies should include sham-control groups and focus on specific target patient population, types and location of LBP. These studies should also focus on clinically relevant outcome measures such as activity of daily living and functionality (e.g., return to work).

Chronic Neck Pain

The design of many of the clinical studies focusing on the therapeutic effect of acupuncture and other forms of acustimulation on chronic neck pain is similar to that of LBP. Irnich et al. conducted a sham-controlled RCT that compared acupuncture with massage therapy for treatment of chronic neck pain.[27] The investigators found that although true acupuncture was superior to massage therapy it was not superior to sham acupuncture. After the publication of this study in the *British Medical Journal*, a letter to the editor by Vickers suggested that data analysis of the study was not acceptable and that the original data had to be reanalyzed.[28] Indeed, after reanalysis of the data, Vickers suggested that acupuncture was superior as compared to massage and sham therapies as a short-term treatment for chronic neck pain. Vickers and Irnich next collaborated in a sham-RCT study that compared acupuncture needle placement at acupuncture points to local trigger points and to sham laser acupuncture. They found that stimulation at acupuncture points is superior to both direct needling of local trigger points and laser sham acupuncture for improving motion-related pain and range of movement in chronic neck pain patients.[29] This study examined, however, only the immediate effects of acupuncture on neck pain (15–30 min). A similar study was conducted using true and sham acupuncture needling applied directly to local trigger points in patients who suffered from chronic neck and shoulder pain.[30] The investigators found that although acupuncture provided greater immediate relief for the neck and shoulder pain there were no long-term benefits.[30] White et al.[31] conducted a sham-controlled crossover study to explore whether the location of the PNT has an effect on the immediate analgesic responses in patients who suffer from chronic neck pain. These investigators found that local (versus remote) dermatomal needling produced greater improvement in the analgesic response, as well as both physical and mental performance, as assessed by a well-validated functional inventory, the SF-36.

Sator-Katzenschlager et al.[32] compared the efficacy of six weekly treatments of manual and auricular EA for the treatment of chronic neck pain (Fig. 1). The investigators found that auricular EA is superior to manual auricular acupuncture in reducing the severity of pain, analgesic consumption, and return to full-time employment. In a large-scale trial that was conducted in the United Kingdom, patients were randomized to receive either TEAS or sham-TEAS. Eight treatments were administered over a 4-wk period and outcome assessments included neck pain, the neck disability index, the SF-36, and analgesic consumption. This study found that patients in the TEAS group reported significantly less pain when compared with patients in the sham-TEAS group.[33] However, neck disability index and SF-36 scores did not differ significantly between groups. Finally, a small-scale sham-RCT was conducted with 24 subjects who suffered from chronic neck and shoulder pain.[34] Subjects were randomized to receive either 10 acupuncture or sham-acupuncture treatments combined with daily acupressure at acupuncture points or at sham points over a 3–4 wk period. After this very intensive regimen, the investigators found that at the 6 mo and 3 yr

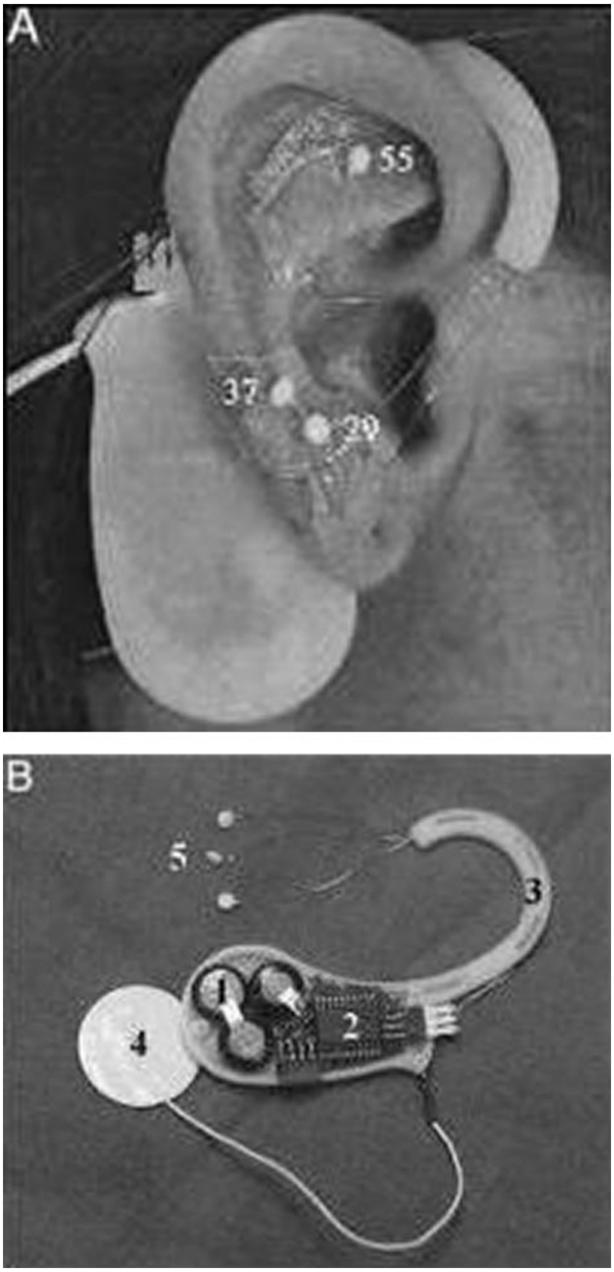

Figure 1. A, acupuncture points are indicated by bullets and numbered according to the nomenclature of Nogier[5]: cervical spine,[37] shen men,[55] and cushion.[29] B, The electrical point stimulation device P-STIM™. Reproduced with permission from Sator-Katzenschlager S, Szeles J, Scharbert G, Michalek-Sauberer A, Kober A, Heinze G, Kozek-Langenecker S. Anesth Analg 2003; 97:1469–73, © Lippincott Williams & Wilkins.

follow-up evaluations patients in the acupuncture group had better sleep quality, less anxiety and pain, less depression, and a higher satisfaction with life when compared with patients in the sham group.[34] In contrast to the above studies, a crossover study by Zhu and Polus indicated that there are no differences in either subjective or objective measures between true and sham acupuncture treatments for chronic neck pain.[35] Analogous to the studies in patients with chronic LBP, studies indicate that PENS and PNT are effective short-term treatments for chronic neck pain. Preliminary data suggest that acustimulation may establish the efficacy of acupuncture as a long-term treatment for chronic neck pain. We submit that additional studies are needed to determine the duration and strength of pain relief compared with established therapies and the underlying physiologic mechanism of acupuncture-induced analgesia in chronic neck pain.

OA of the Knee

Although acupuncture is commonly used as a treatment for OA of the knee,[36] a systematic review published in 2001 found inconsistent results and insufficient evidence to determine whether acupuncture is superior to sham treatment.[37] However, Berman et al.[38] investigated the efficacy of acupuncture as an adjunctive therapy in elderly patients suffering from OA of the knee using a randomized crossover study design. These investigators found that patients randomized to acupuncture treatments had improved on both McMaster University's OA index and Lequesne's indices at 4 and 8 wk. The same research team then conducted a large-scale sham-controlled RCT that included 570 patients that were randomized to receive acupuncture treatment, sham treatment, or an educational intervention over a 6-mo period.[39] The research team found that patients in the acupuncture group experienced significantly greater improvement than the sham group in both McMaster University's OA index function and pain scores. A sham-controlled RCT published in *Lancet* randomized patients with OA of the knee to receive 8 wk of acupuncture, sham, or waiting list control. The study found that patients in the acupuncture group experienced improved joint movement and significantly less pain. However, a follow-up at 1 yr revealed no differences among the various study groups.[40]

We conclude that the use of acupuncture stimulation is an effective short-term treatment of OA of the knee. Unfortunately, long-term benefits from acupuncture treatment have not been demonstrated.

Dental-Related Pain

A systemic review published in 1998 in the *British Dental Journal* suggested that acupuncture could alleviate pain after dental procedures.[41] In 1999, a randomized, double-blind, placebo-controlled trial conducted by Lao et al. reported that the average pain-free postoperative time and time to requested pain medication was longer in patients who received true versus sham acupuncture during wisdom tooth extraction.[42] Kitade and Ohyabu[43] performed a study to examine patients who underwent mandibular wisdom tooth extraction using local anesthesia versus a combination of local anesthesia and low-frequency electrical acupuncture at bilateral LI4 ("He Gu" the 4th acupuncture point along the large intestine meridian), unilateral at ST6 ("Jia Che" the 6th acupuncture point along the stomach meridian) and ST7 (Xia Guan the 7th acupuncture point along the stomach meridian) acupoints (ipsilateral to the surgical side). The investigators found that EA significantly decreased the magnitude of postoperative pain. A large-scale study by Bausell et al.[44] was designed to explore the effect of "expectancy" in acupuncture analgesia on postprocedural dental pain. The investigators found that, although there was no statistically significant analgesic effect between the acupuncture and placebo groups, participants who believed they received "real" acupuncture reported significantly less pain than those who believed they had received a placebo.

We conclude that data regarding the use of acupuncture analgesia for the management of acute dental pain is inconclusive and that future studies should consider the issue of "expectancy effect."

Procedural Analgesia

Acupuncture and related techniques have been used during medical procedures, such as colonoscopy. Wang et al.[45] demonstrated that pain, serum β-endorphins, epinephrine, norepinephrine, and dopamine levels were similar between patients who received EA (ST36-Zusanli, ST37-Shangjuxu; the 36th and 37th acupuncture points along the stomach meridian, auricular Shenmen point) and patients who received meperidine during colonoscopy procedures. These investigators also found that patients receiving EA had fewer side effects such as dizziness. Since these investigators did not include a sham-control group, their findings should be interpreted cautiously. Fanti et al.[46] conducted a sham-RCT to evaluate the analgesic effects of EA in a group of patients who were undergoing colonoscopy procedures. Patients in both the acupuncture and sham groups received the same frequency (100 Hz) of stimulation for the 20 min before the procedure and throughout the duration of the procedure. The investigators found that patients in the acupuncture group reported nonsignificantly reduced pain during the procedures.

Therefore, currently available data do not support the use of acupuncture as an analgesic adjuvant during colonoscopy.

Surgical Anesthetic and Anecdotal Analgesic–Sparing Effects

Anecdotal reports from China indicate that acupuncture can be used successfully as a sole anesthetic in a variety of surgical procedures such as open-heart surgery.[47] However, whether acupuncture can be used as a sole anesthetic or as an adjunct to local and general anesthesia in the Western world remains to be determined. Schaer[48] conducted a study in which women undergoing gynecological procedures that required general anesthesia were randomized to receive either fentanyl or EA for intraoperative analgesia. The investigator found that EA was as effective as 0.27 μg/kg of fentanyl given IV every 10 min. Greif et al.[49] performed electrical stimulation at the lateralization-control point near the ear tragus and reported that this intervention significantly decreased the desflurane anesthetic requirements (approximately 25%). Similarly,

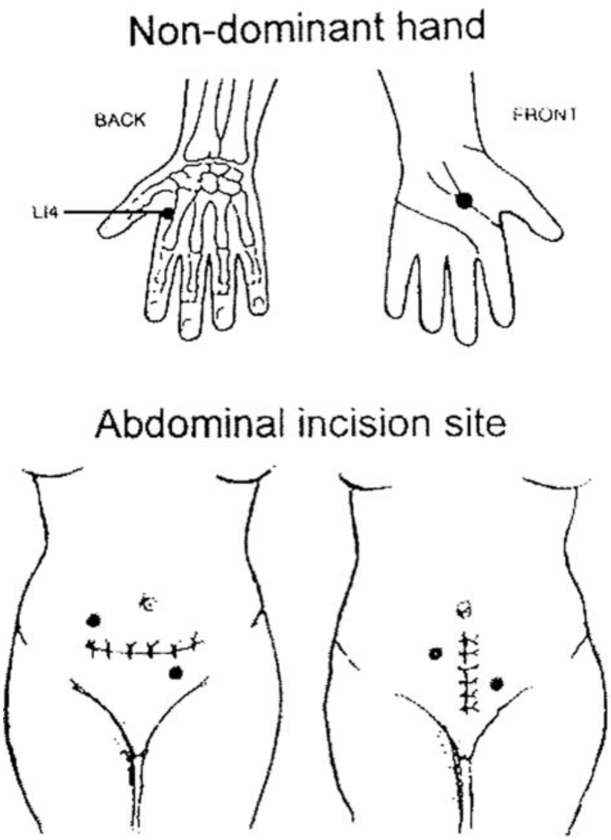

Figure 2. The locations of electrodes at Hegu (LI4) and the thenar eminence as well as at either side of the surgical incision. Reproduced with permission from Wang B, Tang J, White PF, Naruse R, Sloninsky A, Kariger R, Gold J, Wender RH. Anesth Analg 1997; 85:406–13, © Lippincott Williams & Wilkins.

Taguchi et al.[50] who applied auricular acupuncture stimulation at Shenmen, thalamus, tranquilizer, and master cerebral points also observed a similar anesthetic-sparing effect.

In contrast, Sim et al.[51] conducted a sham-controlled RCT study of EA in a group of women scheduled for lower abdominal surgery. The women were randomized to receive preoperative EA or sham EA, or postoperative EA at ST36 and PC6. The investigators found no difference when preoperative EA was compared with preoperative sham EA; more importantly, postoperative patient-controlled analgesia morphine consumption was not different among the three treatment groups. Similarly, Morioka et al.[52] found that EA failed to decrease desflurane anesthetic requirements, and Kvorning et al.[53] found that EA actually increased sevoflurane anesthetic requirements.

Based on these contradictory data, it is reasonable to conclude that the effect of intraoperative acupuncture analgesia remains controversial. In future studies, it is also necessary to standardize the type and depth of anesthesia and opioid analgesic usage, as well as the duration of stimulation. These conflicting results can be partially explained by suppression of acupuncture-induced blood oxygen level-dependent (BOLD) signals observed under general anesthesia.[54] Acupuncture-induced BOLD signals are the magnetic signals generated

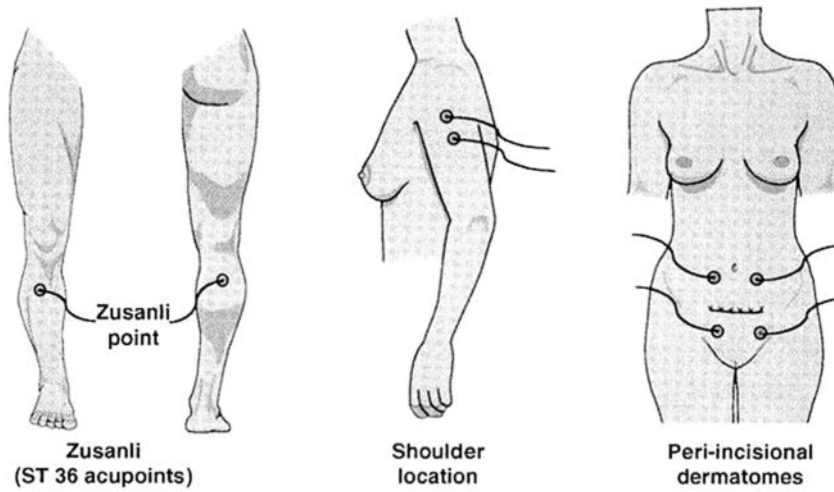

Figure 3. The location of transcutaneous electrodes at acupuncture point Zusanli (ST36) and non-acupuncture point and at the either side of incision. Reproduced with permission from Chen L, Tang J, White PF. Anesth Analg 1998;87:1129–34, © Lippincott Williams & Wilkins.

by the ratio of oxyhemoglobin and deoxyhemoglobin in the areas of the brain where there are hemodynamic changes related to acupuncture stimulation. In other words, acupuncture-induced BOLD signals are an indirect measure of neuronal activities at the regions of the brain affected by the acupuncture stimulation.

Acute Postoperative Pain

Manual Acupuncture Techniques

In a sham-controlled RCT, Kotani et al. applied intradermal needles to "Back Shu" acupoints in a group of patients who were scheduled to undergo major abdominal procedures.[55] These acupuncture needles were inserted 2 h before induction of anesthesia and retained in place for 48 h postoperatively. The investigators found that patients in the acupuncture group reported a significant reduction in postoperative pain and analgesic requirements and postoperative nausea and vomiting compared to the sham group. Usichenko et al.[56] examined the analgesic effects of auricular acupuncture in a group of patients who underwent total hip arthroplasty. Sixty-one patients, who were scheduled to have total hip arthroplasty, were randomized to receive either auricular acupuncture or sham (auricular) acupuncture perioperatively. The acupuncture semipermanent press needles were placed the evening before surgery and retained for 36 h postoperatively. The investigators found that analgesic consumption during the first 36 h postoperatively was lower in the auricular acupuncture when compared with the sham group. In contrast to the above positive studies, Gupta et al.[57] conducted a sham-controlled RCT to evaluate the effect of intraoperative acupuncture intervention on the analgesic requirement after knee arthroscopy. The investigators were not able to demonstrate a reduction of postoperative analgesic effect in the acupuncture treatment group. In examining these and other studies, one can conclude that acupuncture is effective in decreasing the severity of postoperative pain, only when the acupuncture stimulation was performed before induction of anesthesia and/or during the postoperative period.[56,58–61] In contrast, acupuncture administered while the patient was under general anesthesia was found to be ineffective in decreasing postoperative analgesic requirement.[57,62]

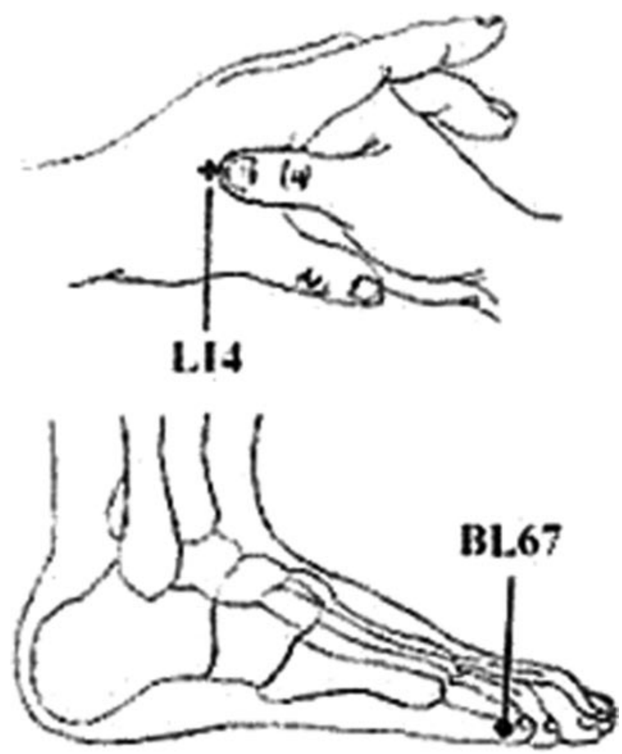

Figure 4. The acupuncture points for labor pain. Reproduced with permission from Chung U, Hung L, Kuo S, Huang C. JNR 2003;11:251–60, © Taiwan Nurses Association.

Electroacustimulation

In 1989, Christensen et al.[58] conducted a RCT involving 20 healthy women who underwent gynecological surgery and received either EA or no treatment (control). The intervention was administrated while these women were emerging from general (volatile)

Table 1. Acupuncture Points Used for Various Acustimulation Techniques in the Management of Acute and Chronic Pain Syndrome

	Acupuncture points	References
Lower back pain		
Body acupuncture		
Large intestine meridian	4, 11	16
Urinary bladder meridian	23, 24, 25, 26, 28, 31, 32, 34, 40, 51, 57, 60	16, 17, 24
Governing vessel meridian	3, 4	17, 24
Spleen meridian	6	17
Ear acupuncture		
Os sacrum		17
Parasympathicus		17
Nervus ischiadicus		17
Lumbar sacrum		17
Shenmen		17, 23
Kidney		17
Lumbar spine		23
Neck pain		
Body acupuncture		
Small intestine meridian	3	27, 29
Kidney meridian	27	27, 29
Lung meridian	7	27, 29
Urinary bladder meridian	60	27, 29
Conception vessel meridian	21	27, 29
Governing vessel meridian	14,20	27, 29
Large intestine meridian	4	27, 29
Ear acupuncture		
Cervical spine		27, 29
Stellate ganglion		27, 29
Osteoarthritis of the knee		
Body acupuncture		
Gallbladder meridian	34, 39	38, 39
Spleen meridian	6	38, 39
Stomach meridian	35, 36	38, 39
Kidney meridian	3	38, 39
Bladder meridian	60	38, 39
Colonoscopy		
Body acupuncture		
Large intestine meridian	4	46
Stomach meridian	36, 37	45, 46
Spleen meridian	6, 9	46
Surgical analgesia		
Body acupuncture		
Stomach meridian	36	52, 53
Spleen meridian	6,9	52, 53
Large intestine meridian	4	53
Pericardium meridian	6	53
Liver meridian	3	53
Urinary bladder meridian	60	53
Ear acupuncture		
Shenmen		50
Thalamus		50
Tranquilizer point		50
Master cerebral		50

Table 1. (continued)

	Acupuncture points	References
Postoperative pain		
Body acupuncture		
Stomach meridian	34, 36	53,56,57
Large intestine meridian	4	53, 54
Governing vessel meridian	2,4	54
Urinary bladder meridian	18–26 and 32	51, 54
Spleen meridian	6, 9, 10	53, 54
Ear acupuncture		
Hip joint		52
Shenmen		52
Lung		52
Thalamus		52
Labor pain		
Body acupuncture		
Lung meridian	7	60
Gall bladder meridian	25, 26, 27, 28, 29	60
Urinary bladder meridian	25–36, 54, 67	60, 61
Conception vessel meridian	2,3	60
Large intestine meridian	4	60, 61
Spleen meridian	6	60, 62

anesthesia but received 70% nitrous oxide to block recall of the intervention. Postoperatively, the investigators found that patients who received EA consumed significantly less (40%) pethidine in the postanesthesia care unit when compared with the control group. In a follow-up RCT, these researchers administered continuous EA from the preoperative period throughout the intraoperative period.[61] In contrast to their previous findings, the investigators found no differences in the postoperative analgesic consumption between the acupuncture and control groups.[61] This reported inconsistency may have been a result of the development of tolerance to prolonged acupuncture stimulation[62] and/or a direct suppression of acupuncture-related BOLD signals by general anesthesia.[54] These data are consistent with studies examining the efficacy of acupoint stimulation for the prevention of postoperative nausea and vomiting. For example, White et al.[63] found that acupoint stimulation was only effective when administered after surgery.

In 1997, Wang et al.[59] conducted a sham-controlled RCT evaluating the analgesic effect of postoperative TEAS in patients undergoing lower abdominal surgery (Fig. 2). Following a standardized anesthetic protocol, TEAS was applied either to acupuncture points or the para-incisional dermatomes, with the intensity of the electrical stimulation delivered high (9–12 mA) or low (4–5 mA) level. The investigators found that TEAS treatment of these locations resulted in a 30%–35% reduction in the postoperative opioid analgesic requirements. They also found that high-intensity TEAS was more effective in decreasing postoperative analgesic requirement than low-intensity

Table 2. Summary of the Evidence Supporting the Use of Acupuncture and Related Forms of Acustimulation in the Management of Chronic Pain Conditions

Condition	Interventions	Reference (1st author/no.)	No. of subjects (*N*)	Postintervention (*P*) <1 mo	1–3 mo	3–6 mo	6–9 mo	9–12 mo	3 yr
Low back pain	Acupuncture	Carlsson/16	50		<0.05	<0.05			
	Acupuncture	Leibing/17	133		0.0009		0.068		
	Acupuncture	Molsberger/18	124		<0.00003				
	PENS	Ghoname/19	60	<0.02					
	PENS	Ghonmae/20	68	<0.01					
	PENS	Hamza/21	75	<0.001 for 30 min and 45 min					
	PENS vs. TENS	Yokoyama/22	60	<0.01	NS				
	Auricular Acupuncture	Sato-Katzenschlager/23	87		0.007				
	Electroacupuncture	Meng/24	55	0.001	0.007				
Neck pain	Acupuncture	Irnich/Vicker reanalysis/27,28	177	0.031					
	Acupuncture	Irnich/29	36	0.014					
	Acupuncture	Nabeta/30	34	<0.01					
	PNT	White/31	68	<0.001 for local dermatome					
	Auricular Acupuncture	Sato-Katzenschlager/32	21	<0.05	<0.05				
	Acupuncture	White/33	135	0.01					
	Acupuncture+pressure	He/34	24			<0.04			<0.001
	Acupuncture	Zhu/35	29	<0.05	>0.05				
Osteoarthritis of the knee	Acupuncture	Gaw/36	40	<0.05 before and after >0.05 between true and placebo					
	Acupuncture	Berman/38	73	<0.001					
	Acupuncture	Berman/39	570		0.01		0.01		
	Acupuncture	Witt/40	294	<0.001		0.063		0.080	

PENS = percutaneous electrical nerve stimulation; TENS = transcutaneous electrical nerve stimulation; PNT = percutaneous neuromodulation therapy.

TEAS. Chen et al.[11] conducted a similar study with surgical patients randomized to receive TENS at one of three locations: an acupuncture point, a nonacupuncture point, or at the dermatome corresponding to the surgical incision (Fig. 3). They found that both TENS at the acupuncture point and TENS at para-incisional dermatomes were effective in producing a similar analgesic-sparing effect after surgery. Importantly, simultaneous stimulation at both acupoints and dermatomes resulted in additive opioid-sparing effects. Lin et al.[60] performed a large scale RCT to examine the effects of various frequencies of preoperative EA on postoperative pain and opioid-related side effects. Analogous to previous investigations,[11,60] They found that the postoperative analgesic effect is positively correlated to the frequency of the electrical stimulation. That is, 100 Hz of EA resulted in less analgesic consumption in the first 24 h postoperatively.

In conclusion, acupuncture is effective as an adjunctive treatment for acute postoperative analgesia if administered to surgical patients in the postoperative period. Future studies should examine whether the efficacy of EA and related forms of acustimulation is influenced by the depth of anesthesia, types of anesthetics (i.e., IV versus volatile), and different states of anesthesia or types of anesthetics. It also seems that the analgesic effect of electro-analgesia is affected by the duration, amplitude, and frequencies of stimulation. Location of electrode placement plays a less significant role in the analgesic effect as long as the placement of electrodes is either at an appropriate acupuncture point or at the peripheral nerves corresponding to the surgical incision.[11]

Labor Analgesia

Ramnero et al.[64] conducted a nonblinded RCT study to evaluate the efficacy of acupuncture as an analgesic adjuvant during labor. These investigators found a decreased requirement for meperidine in the acupuncture group compared with a control group with the same parity. Chung et al.[65] conducted a sham-controlled RCT study to determine the effect of acupressure on labor pain and uterine contractions during the first stage of labor (Fig. 4). These investigators found that during the first stage of labor the patients who received acupressure reported significantly less labor pain compared to patients who received sham or no treatment. Moreover, there was no significant difference in uterine contractions during the first stage of labor among the three groups. Finally, Lee et al.[66] performed a sham-controlled RCT to evaluate the analgesic effects of acupressure on labor pain and time to delivery. These investigators reported that labor pain score during the first hour after

Table 3. Summary of the Studies for Acute Conditions

Condition	Interventions	Reference (1st author/no.)	No of subjects (*N*)	Postintervention (*P*)
Dental analgesia	Acupuncture	Lao/42	39	0.01
	Electroacupuncture	Kitade/43	44	<0.05
Colonoscopy	Electroacupuncture	Fanti/46	30	0.01
Surgical analgesia	Electroauricular acupuncture	Greif/49	20	<0.001
	Auricular acupuncture	Taguchi/50	10	0.003
	Electroacupuncture	Sim/51	90	Postoperative 6–12 h, $P = 0.015$; total 24 h, $P > 0.05$
	Electroacupuncture	Morioka/52	14	0.08
	Electroacupuncture	Kvorning/53	46	>0.05
Postoperative pain	Acupuncture intradermal	Kotani/55	175	<0.05
	Auricular acupuncture press	Usichenko/56	54	0.004
	Acupuncture	Gupta/57	42	>0.05
	Electroacupuncture	Christensen/58	20	2 h postoperative, $P = 0.007$, 6 h postoperative, $P = 0.058$
	TAES	Wang/59	101	24 h postoperative, $P < 0.05$ for low and high TAES
	Electroacupuncture (high vs. low)	Lin/60	100	<0.05 for first request of pain medicine, total analgesic requirement for the 24 h postoperative
	Electroacupuncture	Christensen/61	50	>0.05
Labor pain	Acupuncture	Ramnero/64	46	<0.05
	Acupressure	Chung/65	127	0.041
	Acupuncture	Lee/66	75	$P = 0.021$ for pain reduction, $P = 0.006$ for duration of labor

TAES = transcutaneous acupoint electrical stimulation.

the intervention was lower and the total labor time (i.e., delivery time) was significantly shorter in the acupressure versus sham-control group. Therefore, available data indicate that acupuncture and related techniques may be effective for the early stage of labor. However, more data are needed to establish the effectiveness of acustimulation techniques during the entire labor process.

SUMMARY

This article summarizes the current peer-reviewed literature related to the analgesic effect of various forms of acustimulation. Indeed, acupuncture appears to be most effective for short-term management of back pain, neck pain and OA involving the knee. Data regarding the efficacy of acupuncture for dental pain, perioperative pain and colonoscopy pain are inconclusive. Although there are only a few studies examining the efficacy of acupuncture during labor, it seems that acupuncture and related techniques are effective only for stage I labor.*

Any discussion that involves acupuncture-related research is not complete without addressing some of the methodologic issues in this area. Similar to other clinical studies, some acupuncture studies are hindered by inappropriate sample size, confounding variables, poorly defined outcomes, invalidated outcome measures, and inadequate follow-up. Acupuncture research does, however, present additional hinderances such as acupuncturist positive expectancy bias. Although the use of sham is widely recommended in the literature, this technique is not without problems. Insertion of a needle in a nonacupuncture point may result in unexpected physiological results, such as changes in pain thresholds and unintended release of endorphins. The development of a sham-needle may be a solution to the above issue; however, it is difficult to blind the patient and acupuncturist because the presentation of how an acupuncture needle is secured into the acupuncture point and sensation of acupuncture stimulations are different from true acupuncture stimulation. The quest for a matching sham control, one that is inert and identical in appearance and sensation is continuing. Also, the use of subjective De Qi sensation experienced by acupuncturists and patients poses a significant challenge for researchers. There remains a need for well-designed, sham-controlled clinical trials to evaluate the role of acupuncture and related

*We refer the reader to www.yinyanghouse.com for an anatomical drawing of the locations of specific acupuncture points. The reader should note that acupuncture points used in the different studies described in this review appear in Table 1 and therapeutic effects of acupuncture analgesia for various acute and chronic clinical entities discussed in this paper are summarized in Tables 2 and 3.

acustimulation analgesic techniques in the management of acute and chronic pain syndromes. These future studies should also include outcome measures such as patient well-being and resumption of normal activities.

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