How to Use E-Stim with Acupuncture, and why it Works

A Five CEU Hour Course © By Dr. Harvey Kaltsas, A.P., Dipl. Ac. (NCCAOM)
This course will cover the following topics, but they will necessarily be fully compartmentalized as listed below:

1. Instruction in operating battery operated, alternating current, electrical stimulators of milliamp power in a clinical setting for pain control, addiction control, and muscle spasms – including placement and types of clips, and settings of controls: modes, wave forms, frequencies, time, and intensity.

2. Discussion of contraindicated points, frequencies, intensities, and equipment.
   a. The neurochemical and physiologic basis of acupuncture analgesia
   b. Progress in the pharmacological studies of acupuncture analgesia
   c. Progress in the use of acupuncture since the 1970’s
   d. Resources to learn more about electroacupuncture

**PART 1.**

After showing a recent graduate of an acupuncture college how to treat a sciatica patient with e-stim using a Pantheon Research model 4-C Electro-Stimulator, I was surprised when she asked, “How do you know which needle gets the red clip and which gets the black clip?” She then explained that her Chinese instructors in school always made a big deal about which clip goes where.

This got me to thinking, “Just how little do practitioners know about how to use electrical stimulators, and what kind of stimulators are other practitioners using?” I thought this because there is no basis in electronics or human physiology for differentiating between the red and black clips when using a stimulator that delivers an alternating current (AC), perfectly balanced, biphasic square wave, the type of stimulator that should be found in most acupuncture clinics. More on this later.

To launch right into this topic, I presume and pray that no one is attaching clips from stimulators that deliver net direct current (DC) onto acupuncture needles. Except when treating cancerous lesions with electro-cancer therapy (ECT), in itself a serious topic for lengthy study, such DC stimulators should only be used with TENS electrode pads or with a hand held ground and a metal or moistened Q-tipped probe which rests on the skin’s surface.

**Why avoid using a DC stimulator hooked to needles?** The answer is simple. It damages the needles, and you run the risk of breaking them off inside the patient. Running DC or direct current from one acupuncture needle to another creates a migration of electrical ions from one needle to the other. This is what happens with electrolysis or electroplating. Metal ions from a negatively charged electrode transport through a fluid medium (in this case human tissue) to a positively charged electrode, and metal builds up on the positively charged electrode. In practical terms, this means that the needle with the black clip attached gives up pieces of metal which then wind up attached to the needle with the red clip. The black clipped needle becomes porous and weak and can break off inside the patient when retracted. The red clipped needle is both weakened and has metal plated to its side in a jagged, irregular fashion and can rip out human flesh when withdrawn. It’s not a pretty sight.

In addition, when subjected to enough percutaneous DC current, the water in human tissue begins to break down into constituent molecules. Hydrochloric acid (HCL) and oxygen gas bubbles form in the tissues on the way to and around the positive (red) electrode or needle, and sodium hydroxide (NaOH) and hydrogen gas bubbles form around the negative (black) electrode or needle.

Drs. Gabriel Stux and Bruce Pomeranz discuss the matter of DC currents and biphasic square waves in their book *Basics of Acupuncture*, 1998, pp. 272-273:
“Generally the red lead of each pair of wires is positive, and the black is negative. Pulses of electricity are applied to the needles in order to stimulate nerves, with the pulse being from 0.1 to 1.0 ms [milliseconds] in duration (some stimulators have adjustable pulse width). More expensive, elaborate stimulators use biphasic pulses (negative followed by positive or vice versa) in order to reduce polarization of each needle due to electrolysis. (The negative pulse cleans the electrode of electrolytes deposited by the preceding positive pulse.) **If the pulses are perfectly biphasic, then the net DC current is zero and no polarization occurs.** Polarization is a nuisance as it raises the electrode resistance over time, thus reducing the intensity of stimulation. Also, it can cause the needle to break off in the tissue.

“Another advantage of biphasic pulses is that the two needles of each pair receive symmetrical stimuli (one needle being the mirror image of the other). Hence the red lead has a positive pulse followed immediately by a negative pulse, while the black lead has a negative pulse followed by a positive pulse. Since negative pulses cause an action potential on the nerve, it is important that both needles in a pair receive negative pulses, which is only possible in a biphasic stimulator. The intensity of stimulation is under the control of the intensity knob. In less expensive stimulators in which the biphasic pulses are not perfectly matched (the negative wave is not equal to the positive wave), the negative black lead will give a stronger needle sensation than the positive, red lead. In order to achieve an optimum effect for acupuncture analgesia, the strongest tolerable intensity is required for De Qi (to activate type II and III muscle nerves). **If both leads of a pair deliver symmetrical, biphasic pulses then both needles will be optimally stimulated to give De Qi.** With less expensive devices, however, only one needle of a pair is adequately activated (the needle attached to the black lead).”

**ELECTRO-CANCER THERAPY WITH DC GALVANIC STIMULATORS:**

DC or galvanic stimulators do have their place in the practice of acupuncture, but it is a very selective application requiring specialized training. Since 1988 the practice of ECT has spread widely throughout China. In 1992 one researcher, Dr. Xin Yu-Ling, MD, published a report documenting his results treating 2516 patients, and by 1993 it was already being used in 818 Chinese hospitals.

An ECT session resembles a normal electro-acupuncture treatment, but with some differences. The physician inserts a platinum or gold needle into the center of the tumor and attaches a positive, red clip from a galvanic (DC) stimulator. The physician then places silver needles around the tumor with negative, black clips attached, no farther than 1.5 centimeters apart. Voltages of 6 to 15 volts are used, dependent upon tumor size. The most common size of tumor treated is about 3 to 5 centimeters in diameter. Tumors as large as the 5 to 10 centimeter range have been killed with ECT.

Running current and silver ions into the tumor changes the pH within the tumor and basically cooks it, creating heat shock proteins which help the immune system to identify similar cancer cells around the body. In this way, ECT treatment of a local breast tumor can kill a distant metastatic liver tumor.

In China, Dr. Xin Yu-Ling, MD and his associates treated a wide variety of cases with impressive results. At the First International Conference of Bio-Electrotherapy for Cancer held in Beijing in 1992, Dr. Xin reported the following: more than 35% of cases were put into full remission; 43% had partial remissions; 15% showed no change; and in only 7% of the cases did the disease progress during therapy. (See Table 1).

**Table 1.** Cancer Reduction Efficacy of Bio-Electrotherapy as Experienced by the Administering Oncologists in China - Results from Applying Galvanotherapy to Chinese Cancer Patients
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Patient Load Number (#)</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>CR+PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2516</td>
<td>885</td>
<td>35.2</td>
<td>1080</td>
<td>42.9</td>
<td>379</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>593</td>
<td>168</td>
<td>28.3</td>
<td>298</td>
<td>50.3</td>
<td>76</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>389</td>
<td>98</td>
<td>25.2</td>
<td>196</td>
<td>50.4</td>
<td>74</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>366</td>
<td>244</td>
<td>65.8</td>
<td>95</td>
<td>26.0</td>
<td>20</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>288</td>
<td>78</td>
<td>27.1</td>
<td>82</td>
<td>28.5</td>
<td>59</td>
</tr>
<tr>
<td>Metastatic lymphoma</td>
<td>190</td>
<td>49</td>
<td>25.8</td>
<td>89</td>
<td>46.8</td>
<td>31</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>113</td>
<td>29</td>
<td>25.7</td>
<td>56</td>
<td>49.6</td>
<td>19</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>95</td>
<td>56</td>
<td>58.9</td>
<td>34</td>
<td>35.8</td>
<td>4</td>
</tr>
<tr>
<td>Facial tumor</td>
<td>72</td>
<td>28</td>
<td>38.9</td>
<td>29</td>
<td>40.3</td>
<td>11</td>
</tr>
<tr>
<td>Metastases in breast and abdominal wall</td>
<td>66</td>
<td>17</td>
<td>25.8</td>
<td>25</td>
<td>37.9</td>
<td>15</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>57</td>
<td>20</td>
<td>35.1</td>
<td>24</td>
<td>42.1</td>
<td>9</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>53</td>
<td>11</td>
<td>20.8</td>
<td>34</td>
<td>64.2</td>
<td>5</td>
</tr>
</tbody>
</table>

Key: CR is Complete Remission; NC is No Change; PR is Partial Remission; PD is Partial Deterioration

To put these ECT results from China in proper perspective, the American Cancer Society finds a 5% remission rate in response to chemotherapy to be satisfactorily effective. ECT’s 80% remission rate far surpasses the success rate for any chemical or radiologic therapy used in America.

**Problems with Older Chinese Stimulators:**

Over the past 36 years I have used many types of electrical stimulators, from “the electric aspirin,” a very crude electric stimulator brought over by NESA founder Dr. James Tin Yao So, to the WQ-10-A, WQ-10-B, and WQ-10-C. All these devices were made in China, and all suffered from the same deficiencies. They were four channel stimulators, but the intensity delivered to one channel was not always isolated to that channel. Sometimes intensity would jump from one channel to another, or there would be discontinuous geometric jumps in amplitude when turning up the intensity dial, and patients would get shocked. Even worse, sometimes current would flow at a high rate even if the intensity dials were set at zero, shocking the patients as soon as the machine was turned on.

Also the wave forms were not necessarily 100% biphasic and certainly not perfectly symmetrical biphasic square waves. That is there could be more current flowing in one direction than the other; thus there could be a net DC current delivered, resulting at times in electrolysis of the needles. Perhaps this is why the convention originated in the 1970’s and 1980’s to attach the black alligator clip to the distal points and red clips to the more proximal points, with practitioners intuitively understanding that current was indeed flowing from one direction to another and not perfectly back and forth as it should have been. Too often the machines broke, and it was very difficult to get them repaired.

**Preferred Equipment:**

**Stimulators:**

Ultimately, in the early 1990s, I started buying stimulators form Pantheon Research, I believe it to be the only American based manufacturer of milliampere acupuncture stimulators, and all my troubles with stimulators have since gone away. [No, this is not a paid commercial advertisement. I have no financial ties to Pantheon whatsoever]. The channels in the Pantheon stimulators are completely separated, with no intensity jumps possible.
from one channel to another. The wave forms are perfectly symmetrical biphasic square waves, that is the wave form alternates perfectly from positive to negative and negative to positive, obviating any of the aforementioned electrolysis problems associated with DC stimulators. Symmetrical biphasic square waves are also known to be the most comfortable. The machines rarely break down. Of the two machines I own, only one malfunctioned (once) in 18 years – and then it was readily repaired at no cost).

There are several other quality stimulators on the market. Lhasa OMS sells two that employ symmetric biphasic square waves, the ITO ES-160 from Japan and the E600 Han from China. Both have 6 channels, as do some of the excellent Pantheon stimulators. Lhasa also offers three stimulators with asymmetric biphasic square waves designed to minimize electrolysis – the positive side of the wave is a square wave and the negative is a spiked wave. Two are updated versions in the WQ-10 line, the AWQ-105 Pro and the AWQ-104L, and the third is the Model ES-130 from Japan. In my personal experience the Japanese alligator clips are both more expensive and more reliable than the Chinese. This may hold true for the stimulators as well, but I can’t say for sure, since I’ve been using Pantheon’s stimulators for two decades.

**CLIPS:**

There are basically three styles:

1. Alligator clips
2. MicroClips™ and micro duck beak clips
3. Micro-hook clips

I’m old school and still use alligator clips, preferably those made in Japan since they’re more reliable. Sometimes I’ll fashion my own with supplies from Radio Shack. The advantage of alligator clips is this: they are big enough so that those of us with less nimble fingers can handle and attach them easily. The disadvantage is that they are heavier than the MicroClips and duck beak clips which Pantheon and Lhasa OMS also offer, respectively. When necessary I place paper tape on adjacent skin to secure in place the alligator clips which have been attached to needles. Another disadvantage of alligator clips is that if you attach them to the shaft rather than the handle of the needle, the spaces between the teeth are often bigger than the shaft of the needle, and the clip can make intermittent contact with the needle, thereby breaking the flow of electric current intermittently. To overcome this, I never attach the alligator clip to the shaft but only to the handle, which is always thick enough to accommodate the teeth of the acupuncture needle. This also means that I can never use plastic handled needles when using e-stim.

The advantages of the MicroClips and duck beak clips are that they are light – only \( \frac{1}{4} \) as much as standard alligator clips - and grip firmly no matter what diameter the needle shaft may be. The main disadvantage, for me at least, is that the handles are small and are thus unwieldy at times.

Micro-hook clips attach firmly to the shaft of the needle but some may find them to be a little too small (although they still do fit my clumsy fingers), and they tend to break more readily than alligator clips because the wire inserts perpendicularly into the clip. It breaks there on me sometimes.

**WIRES:**

Thicker is better; 28 gauge biomedical wire is light and strong. Between treatments do not crimp the wires or mash into the plugs which stick into the stimulator as the wires may break. I usually hang mine from a high place so they can dangle. Most machines come with a lead tester so you can ascertain if the plug, wire, and clips are functioning properly.
**EAR PROBES WITH HAND GROUNDS:**
These are inexpensive, ubiquitous, and plug into the various stimulators. Lhasa OMS sells their A4 Pen Probe for $8.50. For $35-$45 dollars Lhasa and Pantheon also sell facial stimulation probes to be used with moistened Q-tips heads into the heads of the probes.

**FREQUENCIES AND WAVE FORMS:**
The safest most comfortable wave form to use is a symmetrical biphasic square wave. This wave guarantees that there will be no electrolysis and is the most comfortable for the patient. Patients tend to experience biphasic waves with negative spikes as being a little sharper when amplitude is turned up. Dr. Ji-Sheng Han et alia conducted research into how “High and low frequency electroacupuncture analgesia are mediated by different opioid peptides.” Basically he found that there are three different basic forms of endogenous opioid peptides (EOP’s) involved in acupuncture analgesia:

1. meta-enkephalin (MEK) and leu-enkaphalin (LEK);
2. beta-endorphin (BEP)
3. dynorphin A (Dyn A) and dynorphin B (Dyn B)

Han concluded that “Different kinds of EOP may be released in the spinal cord by EA stimulation of different frequencies,

- MEK at 2 Hz,
- Dyn A at 100 Hz, and
- a mixture of enkephalins and dynorphins at 15 Hz.”

Han further concludes that “BEP and LEK do not seem to play a significant role in the mechanisms of acupuncture analgesia.”

Enkephalins have their greatest effect on the upper body and head, dynorphins on the spine, torso, and extremities. Thus it’s a pretty safe bet when treating the head and neck to use a combination of 2 Hz and 15 Hz and when treating the lower part of the body to use a combination of 2 and 100 Hz.

**PROTOCOLS FOR USE:**

- The first thing you should demand of an electrical stimulator is that it should run only on batteries. If you have a stimulator that needs to be plugged in, beware! There is always the possibility that it could short circuit and deliver a lethal surge of electricity to your patient. For that reason, I would never attach clips from a plugged in stimulator to acupuncture needles in a human body. This is especially true here in Florida where we have an abundance of lightning storms and consequent unexpected power surges.
- Before attaching clips to the needles, be certain that the machine is turned off and that all intensity knobs are turned down to zero. Otherwise you and your patient can be in for quite a shock.
- Make sure the leads for your clips are plugged into the stimulator.
- Attach the clips to the handles of the needles.
- Adjust the frequency on the machine to be appropriate for the area(s) being treated.
- Double check to see that the machine is turned off and that the intensity knobs are dialed down to zero. Then turn the MODE knob on the electro-stimulator to the desired Mode: Mixed, Continuous, or Discontinuous. I almost always use Mixed mode because it allows one to direct two different frequencies at the tissue, preventing the tissue from accommodating to and tuning out the stimulus. Different frequencies create different forms of endogenous opioid peptides (EOP’s) in the body. More varieties of EOP’s are better for effecting pain relief. Continuous stimulation is similar to that produced by persistent pain.
manual manipulation of the needle, and I use it mostly when doing scalp acupuncture – and at 3 Hz. Discontinuous is similar to intermittent manual stimulation.

► Inform the patient which needles you’ll be stimulating first, then turn on the machine, and SLOWLY turn up the intensity knob. I ask the patients to tell me when they start to feel the stimulation, and I bring the intensity to just above the point whereby the patients can feel it -but below the point where the stimulation is uncomfortable.

► Repeat this procedure for every set of wires used.

► After 10 minutes I turn up the intensity again, slightly, so the patient feels the stimulation again, because usually patients adapt to the sensation.

► Generally I stimulate for 10-30 minutes, no less and no more. This duration is based upon research conducted by Dr. Ji-Sheng Han.

► To end the treatment, turn each intensity knob down part way. Then turn each knob down all the way.

► Then turn the Mode knob to off. This is very important for two reasons. First is that leaving the stimulator on will drain the battery. They are nine volt and cost about $3.00 each. Second, turning the machine off assures that when treating your next patient you won’t attach wires to a machine that’s already on!

► Disconnect the clips from the needles.

► Put the stimulator away in a place where the wires can hang freely.

TO TREAT VARIOUS DISORDERS:

1. PERIPHERAL NEUROPATHY –
   I’ve consistently had great results over the years treating the following points with 2 and 100 Hz for 20 minutes set on mixed frequency: the Bafeng points attached to Sp 5, Sp 9, GB 34, GB 40.

2. ADDICTIONS –
   The following two protocols are taken from and refer to the charts in Terry Oleson’s Auriculotherapy Manual. They involve treating with a hand held probe applied to the ear with a ground held by the patient.

   For nicotine stimulate:
   ► Lung 1 (anterior hypothalamus) for 2 minutes @ 80 Hz continuous
   ► Lung 2 (posterior hypothalamus) for 2 minutes @ 80 Hz continuous
   ► Mouth for 30 seconds @ 5 Hz continuous
   ► Palate 1 for 30 seconds @ 80 Hz continuous
   ► Palate 2 for 30 seconds @ 100+ Hz continuous
   ► Point Zero for 30 seconds @ 10Hz continuous
   ► Shen Men for 30 seconds @ 10Hz continuous
   ► Adrenal Gland for 30 seconds @ 20 Hz continuous
   ► Master Sensorial for 30 seconds @ 100+ Hz continuous
   ► Master cerebral for 30 seconds @ 100+ Hz continuous
   ► Irritability for 30 seconds @ 100+ Hz continuous
   ► Corpus Callosum for 30 seconds @ 20 Hz continuous

   For drugs stimulate:
   ► Lung 1 (anterior hypothalamus) for 2 minutes @ 80 Hz continuous
   ► Lung 2 (posterior hypothalamus) for 2 minutes @ 80 Hz continuous
   ► Point Zero for 30 seconds @ 10Hz continuous
Shen Men for 30 seconds @ 10Hz continuous
► Thalamus (Subcortex) for 30 seconds @ 80Hz continuous
► Endocrine for 30 seconds @ 80Hz continuous
► Adrenal Gland 2 for 30 seconds @ 20 Hz continuous
► Master Sensorial for 30 seconds @ 100+ Hz continuous
► Liver for 30 seconds @ 5 Hz continuous
► Kidney 1 for 30 seconds @ 5 Hz continuous
► Kidney 2 for 30 seconds @ 5 Hz continuous
► Brain for 30 seconds @ 80 Hz continuous
► Occiput for 30 seconds @ 10 Hz continuous
► Sexual desire for 30 seconds @ 10 Hz continuous
► Irritability for 30 seconds @ 100+ Hz continuous
► Corpus Callosum for 30 seconds @ 20 Hz continuous

Further on in this course you will find other protocols for treating addictions in the paper written by Dr. Deke Kendall, one of the pre-eminent researchers in the acupuncture profession. His protocols are simpler but also effective.

3. **PAIN CONTROL AND MUSCLE SPASMS:**
   - **Head and neck** – Treat appropriate points @ 2 and 15 Hz mixed for 10-30 minutes
   - **Low back pain** – Treating appropriate points with “Alternating stimulation at 15-Hz and 30-Hz frequencies was more effective than either 4 Hz or 100 Hz in improving outcome measures.”[^3] Actually, I think a mix of 2 and 100 Hz is the most effective approach.
   - **Rest of body** – appropriate points @ 2 and 100 Hz mixed for 10-30 minutes

4. **SCALP ACUPUNCTURE** –
   Treat appropriate points @ 3 Hz for 3 minutes continuous

**PART 2**

**CONTRAINDICATIONS FOR ELECTRO-ACUPUNCTURE[^4]**

► Do not use with pacemakers (potential cardiac problems)
► Do not apply transcranial stimulation (epileptic possibility with 10-13 Hz)
► Do not apply current across the spine, horizontally
► Do not apply stimulation across the chest region
► Do not apply stimulation over the neck region to prevent laryngospasm
► Profound analgesia induced by E-A puts patients at risk of self-injury
► Do not use with imbedded neural stimulators
► Do not treat lower body points during pregnancy, especially during third trimester
► High frequency or high amplitude application may induce stress, which is contraindicated in cases of hypertension
► E-A can oversedate older patients causing risk of falling asleep after treatment. Patient should be driven to and from clinic. [Or caution them in this regard and observe effects from treatment before sending them home]

[^3]: Source reference
[^4]: Source reference
Excess E-a can produce tolerance by depleting serotonin.
Do not apply to benign and malignant tumors

PART 3 - RESEARCH BY DR. JI-SHENG HAN, M.D. AND OTHERS- TO BE FOUND AS ATTACHMENTS

ATTACHMENT 1:
Summary - Neurochemical Basis of Acupuncture Analgesia (AA)

ATTACHMENT 2:
a. The Role of 5-HT in AA and Acupuncture Tolerance
b. 5-HT Is an Important Mediator for Both High and Low Frequency Electro-Acupuncture Analgesia (EAA)

ATTACHMENT 3:
a. GABA: Antagonistic Effect on EAA
b. Changes in Opioid Activity in Brain and Pituitary during EAA in the Rat
c. Central 5-HT, Opiate Like Substances (OLS) and AA
d. High and Low Frequency EAA Are Mediated by Different Opioid Peptides
e. Analgesia Produced by Electroacupunture of Different Frequencies are Mediated by Different Varieties of Opioids in the Spinal Cord
f. New Evidence Supporting Differential Release of Enkephalin and Dynorphin by Low and High Frequency EA Stimulation

ATTACHMENT 4:
Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies by J.S. Han, M.D.

ATTACHMENT 5:
Percutaneous Electrical Nerve Stimulation (P.E.N.S.) for Lower Back Pain by El-sayed Ghoname, M.D. et al.

ATTACHMENT 6:
Treatment of Substance Addiction with Acupuncture by D.E. Kendall, OMD, Ph.D., L.Ac.

ATTACHMENT 7:
The Effect of Stimulus from the Analgesic Response to P.E.N.S. in Patients with Low Back Pain by E. Ghoname, M.D. et al.
FOR WHAT THEY’RE WORTH -
GLEANINGS FROM AND MUSINGS ON THE RESEARCH OF DR. JI-SHENG HAN:

GABA is an antagonist to both electroacupuncture analgesia (EAA) and to morphine analgesia. Because diazepam facilitates GABA transmission it also results in a marked attenuation of the EAA effect.

Serotonin (5-HT or 5-hydroxytryptamine) augments the effect of electroacupuncture analgesia. Serotonin’s precursor is 5-HP or 5-hydroxytryptophan, which dramatically increases the effectiveness of electroacupuncture analgesia and reverses tolerance to EAA. Thus it makes sense to advise patients in significant pain to supplement with 5-HTP prior to electroacupuncture or finger acupuncture treatment.

Since about “80 percent of the human body's total serotonin is located in the enterochromaffin cells in the gut,” it makes sense to stimulate abdominal points such as K 16; ST 25, 26, & 27; CV 10, 9, 7, 6, 4 for patients with pain.

Electroacupuncture analgesia produces endogenous opiate like substances which act upon the brain at the nuclei accumbens, amygdale, habenula, periaqueductal grey areas, the midbrain, and septum accumbens.

Beta endorphin and ACTH are derived from a common precursor and are co-released from the pituitary under stress.

D-Phenylalanine in rabbits increases the acupuncture analgesia effect of finger acupuncture given to rabbits at the Kunlun point (UB 60) if given 10-15 minutes prior to treatment. D-Phenylalanine is found in breast milk and is available as a nutritional supplement for the treatment of depression and pain. L-Phenylalanine is the artificial sweetener aspartame which has been shown to have neurotoxic effects.

Dynorphin is 6 to 10 times more potent than morphine at producing analgesic effects and is most present in the pituitary, hypothalamus, and spinal cord. Dynorphin’s opioid activity is 50 x more powerful than Beta endorphin, 190 x more powerful than normorphine, and 700 x more powerful than leucinoenkephalin. Dynorphins are readily produced with 10 minutes of electroacupuncture stimulation at 15-100 Hz.

To increase the electroacupuncture analgesia effect, raise the intensity from the electronic stimulator every 10 minutes till 30 minutes. Stimulation beyond 30 minutes tends to diminish the EAA effect.

Cerebral norepinephrine (NE) exaggerates the antagonistic effect to EAA.

The effectiveness of EAA is critically dependent upon the time period of administration of the stimulus. After continuous EAA stimulation for 6-8 hours on rabbits, the EAA effect declined and tolerance developed. However, “Tolerance to EAA was reversed by micro-injection of 5-hydroxytryptophan into nuclei accumbens in the rabbit.”
[1] The Neurochemical Basis of Pain Relief by Acupuncture by J.S. Han, Beijing Medical University, 1987, p. 131

[2] Ibid., p. 333


[5] The Neurochemical Basis of Pain Relief by Acupuncture by J.S. Han, Beijing Medical University, 1987, p.161

[6] Ibid. p. 164

[7] Ibid. p.98


[9] Neurochemical Basis of Pain Relief by Acupuncture by J.S. Han, Beijing Medical University, 1987, p.186

[10] Ibid., p. 219


[12] Ibid., p.368

[13] Ibid., p.373

[14] Ibid., p.411
3.6.

THE ROLE OF CENTRAL 5-HYDROXYTRYPTAMINE IN ACUPUNCTURE ANALGESIA AND ACUPUNCTURE TOLERANCE

J. Tang, S.J. Li, C.W. Xie and J.S. Han
Department of Physiology, Beijing Medical College, Beijing 100083, China.

SUMMARY

The 5-hydroxytryptamine (5-HT) released in the brain and in the spinal cord seem to play an equally important part in mediating the effect of acupuncture analgesia (AA). Profound release of 5-HT for many hours during repeated electroacupuncture stimulation may result in the development of tolerance to 5-HT, which in turn constitutes one of the mechanisms for the induction of acupuncture tolerance (AT).

INTRODUCTION

Serotonergic neurons in the raphe nuclei send ascending fibers to the forebrain and descending fibers to spinal cord. Whereas the descending serotonergic pathway in mediation of AA has been stressed repeatedly1,2, the importance of ascending pathway seems to attract less attention3. In this study 5-hydroxytryptophan (5-HTP), the direct precursor of 5-HT, and cinanserin, the specific antagonist for 5-HT receptors, were injected intracerebroventricularly (ivt) or intrathecally (ith) via chronically implanted cannula to assess the relative importance of 5-HT in brain and the spinal cord for mediation of AA.

It was also interesting to find that while single injection of 5-HTP potentiated AA dramatically, repeated administration of 5-HTP resulted in attenuation of the effect of AA. The possibility of development of tolerance to exogenously administered or endogenously released 5-HT, and its possible implication in the development of AT was thus evaluated.

METHODS

Female rats weighing 180-220 g were used. Nociceptive response was measured by tail flick latency elicited by radiant heat. Electroacupuncture (EA) was applied through two pairs of stainless steel needles inserted into "Zusanli" and "Sanyinjiao" points in both hind legs3. Stimuli of 2-15Hz biphasic electric
pulses of 0.3ms duration were delivered by a 57-6D electronic stimulator. In the first two experiments stimuli of 3V was given for 10 min, while in the later two experiments the amplitude of electric pulses was increased stepwise from 1V to 3V in a period of 30 min. The effect of AA was assessed by the increase in tail flick latency measured after the EA stimulation and expressed as % changes of the basal level, with +150% as the cut-off value.

Ivt injection was performed through chronically implanted stainless steel cannula, and ith injection made via PE10 plastic tubing chronically indwelled in lumbar segment of the spinal cord, the injection volume being 15µl for both ivt and ith administrations.

RESULTS AND DISCUSSIONS

Exp.1. Two groups of 6 rats were given EA stimulation 15 min following the ivt injection of 100µg of cinanserin or 15µl of normal saline. The effect of AA was found to be decreased by 66% in the cinanserin group (p<0.05). Ith injection of cinanserin brought about a 53% decrease in AA (n=8) as compared to the corresponding saline group (n=8, p<0.05). The results were shown in Figure 1.

Fig.1. Changes in the effectiveness of AA following intraventricular(A) or intrathecal(B) injection of cinanserin or 5-HTP in the rat.

Exp.2. It is evident also from figure 1 that the effect of AA was markedly potentiated by 5-HTP in a dose of 200µg either after ivt injection (+54%, p<0.05) or after ith injection (+47%, p<0.05) as compared to the corresponding NS control group.

The results of exp. 1 and 2 clearly indicate the importance of 5-HT in the brain as well as in the spinal cord for mediation of AA.

Exp.3. A group of 12 rats was given 6 consecutive sessions of EA in 6 hr. The effect of AA as shown by the increase in tail flick latency was found to be markedly reduced from the first session to the 6th session. A similar reduction in AA was found in another group of rat in which 6 consecutive ip injections of
5-HTP, 25mg/kg, were given in the same period instead of EA stimulation. The results shown in table 1 suggest that overloading the 5-HT receptors for 6 hr may cause reduction of the effectiveness of 5-HT which in turn caused a reduction in the effectiveness of AA.

**TABLE 1**

The effect of AA after repeated EA stimulation or multiple 5-HTP injections

<table>
<thead>
<tr>
<th>Analgesic effect of EA</th>
<th>N</th>
<th>1st session</th>
<th>last session</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA stimulation ×6</td>
<td>12</td>
<td>110±15%</td>
<td>25±11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-HTP 25mg/kg ip ×6</td>
<td>10</td>
<td>110±9%</td>
<td>41±13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NS ip ×6</td>
<td>8</td>
<td>110±15%</td>
<td>105±11%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Exp.4. The central effects of 5-HT are multiform, one of which is the hypothermic action. A decrease of 1-2°C in rectal temperature was found in rats 30 min after the ivt injection of 12.5µg of 5-HT. This hypothermic effect was found to be significantly attenuated after 6 sessions of EA or 6 ip injection of 5-HTP, implying a reduction in the effectiveness of central 5-HT in these two experimental conditions (Table 2).

**TABLE 2**

The hypothermic effect of 5-HT following repeated EA stimulation or multiple 5-HTP injections

<table>
<thead>
<tr>
<th>Hypothermic effect of 5-HT</th>
<th>N</th>
<th>Control</th>
<th>Post-treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA stimulation ×6</td>
<td>9</td>
<td>1.48±0.12</td>
<td>0.75±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-HTP 25mg/kg ip ×6</td>
<td>11</td>
<td>1.49±0.23</td>
<td>0.58±0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NS</td>
<td>11</td>
<td>1.79±0.31</td>
<td>1.91±0.18</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

The results in exp 3 and 4 provide in vivo evidence of acute tolerance to 5-HT which may have some implications in the development of AT.

Tolerance to endogenously released neurotransmitters such as opioid peptides, 5-HT and NE is a logical consequence for certain physiological or pathological conditions when large amount of neurotransmitters are released continuously for a definite time period. Elucidation of the dynamic course for development of tolerance to different kinds of neurochemical substrates may be of value not only for the understanding of the mechanism of AT, but also of the physiology and pharmacology of chronic stress, certain kind of drug tolerance, etc, as well.

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3.9.

5-HYDROXYTRYPTAMINE IS AN IMPORTANT MEDIATOR FOR BOTH HIGH AND LOW FREQUENCY ELECTROACUPUNCTURE ANALGESIA

ZHANG Min, HAN Jisheng
Acupuncture Research 10(3)212-215, 1985

Evidence obtained from different lines have shown that 5-hydroxytryptamine (5-HT) plays an important role in mediating electroacupuncture analgesia (EAA). However, Cheng and Pomeranz in 1979 reported that p-chlorophenylalanine (pCPA), the specific inhibitor of the 5-HT synthetic enzyme, was effective in decreasing only high frequency EAA, but not the low frequency EAA in the mice. To evaluate whether this is true in the rat, we have used EA of 4 frequencies (2, 15, 100Hz fixed frequency and 2-15Hz changing frequency EA stimulations) and 2 intensities (3V, 9V) to assess the effect of pCPA on EAA.

The effect of EAA in control rats injected with normal saline were rather stable in a period of 2 weeks. Intraperitoneal injection of pCPA (320mg/kg) resulted in a marked decrease (-84% to -90%) of the effect of EAA 3 and 5 days after the ip injection, followed by a gradual recovery which completed in 13 days. The decrease of EAA was of a similar degree whether low or high frequency, weak or strong intensity EA stimulations were used.

It is thus concluded that 5-HT is important in mediating not only high frequency, but also low frequency EA analgesia in the rat.
6.1. GABA: ANTAGONISTIC EFFECT ON ELECTROACUPUNCTURE ANALGESIA AND MORPHINE ANALGESIA IN THE RAT

S.G. Fan, Z.C. Qu, Q.Z. Zhe and J.S. Han

Life Sci 31 (12/13):1225-1228, 1982

(Received in final form June 14, 1982)

Summary

The role of GABAergic system in the brain in mediating electroacupuncture (EA) analgesia and morphine analgesia was studied by using GABA synthesis inhibitors, GABA degradation inhibitors, GABA receptor blockers and diazepam. The results indicate that GABAergic system in the brain may be antagonistic to both EA and morphine analgesia.

There has been increasing evidences suggesting an involvement of GABAergic mechanism in morphine analgesia, although results from different laboratories seemed equivocal(1-4). Very little is known about the implication of GABA in EA analgesia. Our findings in the rat showed that GABAergic mechanism may function to antagonize both EA and morphine analgesia.

Methods

Rats weighing 150-220 g were used. Tail flick latency elicited by radiant heat was measured for testing analgesia. EA was applied via two pairs of stainless steel needles inserted into Zusanli and Sanyinjiao points in both hind legs. A series of dense and sparse (2-15 Hz) electric impulses were delivered by a 57-60 electronic stimulator for 10 min, the amplitude of the main waves being 2V and 3V respectively. The analgesic effect of EA was assessed by the per cent increase of tail flick latency measured after EA as compared with the basal level, with +150% as the cut off limit. The details of nociceptive test and method of EA stimulation were described elsewhere(5).

To test the effectiveness of morphine analgesia, 2 or 6 mg/kg of morphine HCl was injected subcutaneously (sc). Tail flick latency was measured before and 10 min after the drug administration for 1 hr. The per cent changes of the 6 post drug measurements were averaged as the average morphine effect.

intracerebroventricular (icv) Injection of bicuculline or gamma-vinyl GABA was performed through chronically implanted stainless steel cannula or acutely given according to Noble et al(6).

The GABA content in the brain was measured by radioreceptor assay with \(^{3}H\)-baclofen as the radioactive ligand(7,8).

Data were shown as mean±SEM. Significance of difference between groups was determined by t test.
Results and discussions

The effect of 3-mercaptopropionic acid (3-HP) on EA analgesia: 3-HP has been known as a powerful inhibitor of glutamate decarboxylase (GAD) (9), thus reducing the GABA content in the tissue (10). Recently 3-HP was also shown to be a selective inhibitor of GABA release (11). This drug was therefore used as a model compound to reduce the GABAergic function of the brain in the present study. A dose-dependent augmentation of EA analgesia was found 30 min after the intraperitoneal (ip) injection of 3-HP (10, 20, 25 mg/kg) (Fig. 1). Radioreceptor assay revealed a significant reduction of GABA content in brain stem (-19±5%), spinal cord (-37±6%) and cerebellum (-38±5%) after 3-HP administration, while the changes in the diencephalon and forebrain the rest were not statistically significant. These results imply that GABAergic system in brain may have an antagonistic effect on EA analgesia, although the GABA contained in different brain areas may not act in an identical manner.

AOAA (25 mg/kg, ip, 6-8 hr after drug administration) and gamma-vinyl GABA (100ug, icv, 12-24 hr) were used as inhibitors of GABA transaminase (GABA-T) to raise the GABA content in the brain. Both these two drugs elicited marked reduction of EA analgesia. Figure 2 shows a negative correlation between the GABA content in the brain measured 12 hr after gamma-vinyl GABA (25, 100ug) administration and the effect of EA analgesia as indicated by the percent change of tail flick latency after EA stimulation.

AOAA (25 mg/kg, 6 hr) was also shown to reverse the augmentatory effect of 3-HP (25 mg/kg, 30 min) on EA analgesia. On the other hand the antagonistic effect of AOAA (25 mg/kg, 6-8 hr) on EA analgesia was found to be reversed by either isoniazid (200 mg/kg, 45-60 min), the GAD inhibitor, or bicuculline methochloride (0.3ug, icv, 30 min), the GABA receptor blocking agent.

The effect of diazepam on EA analgesia: Diazepam has been shown to facilitate the GABAergic transmission (12). A marked attenuation of EA effect was observed in a group of 19 rats given ip injection of 8 mg/kg of diazepam as compared with the normal saline control group (n=20). This antagonistic effect on EA analgesia could be completely reversed by the GABA antagonist picrotoxin.
has been reducing a selective model study, the intra-receptor (10-19%), while the 15% significantly antagonizing brain

Figure 2 shows a negative correlation between GABA content in the brain and the effect of EA analgesia after gamma-vinyl GABA treatment. Figure 3 shows the antagonistic effect of diazepam (8 mg/kg, ip) on EA analgesia, and the reversal of diazepam effect by picrotoxin (6 mg/kg, ip). N=19-20 in each group.

Parallel results were obtained when morphine was used in stead of EA stimulation: potentiation of morphine analgesia by 3-HP, and attenuation of morphine effect by AOA, gamma-vinyl GABA or diazepam.

Taking all these results together it seems likely that GABA in the brain may function to antagonize the mediation of EA analgesia, and morphine analgesia as well. The mechanism for this phenomenon is not yet known and can only be speculative. It has been shown that serotonin is an important link in mediating both EA analgesia(15) and morphine analgesia(14). It was also reported that the raphe nuclei in the brain stem are tonically inhibited by a GABA system descending from the forebrain structures(15). The possibility seem to exist that the release of GABA in the raphe nuclei may suppress the functional activities of serotonergic system thus reducing the efficacy of EA and morphine analgesia. This hypothesis are currently being evaluated.

We thank Dr. L.L. Iversen and Dr. E. Costa for providing the chemicals used in this study.

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CHANGES IN OPIOID ACTIVITY IN BRAIN AND PITUITARY DURING ELECTROACUPUNCTURE ANALGESIA IN THE RAT

TANG Jian, HAN Ji-Sheng

Journal of Beijing Medical College (3):150-152, 1978

The opioid activity in rat brain and pituitary following electroacupuncture (EA) stimulation was measured by radioreceptor assay (RRA) and correlated with the analgesic effect elicited by EA.

Female rats weighing 200-250 g were given EA to the points Zusanli and Sanyinjiao in both hind legs (2-15Hz, 1-3V, 30 min). EA analgesia was measured and expressed as the percent increase in tail flick latency (TFL). The rat was then decapitated and the brain and pituitary were taken and homogenized in methanol-Tris buffer. The extracts (20-30ul) were incubated with crude brain membrane preparation (300mg/200ul) in the presence of 3H-dihydromorphine (8x10^-4 uCi) for determination of opioid activity, which was expressed as % inhibition of the specific binding of radioligand with membrane preparation.

Opioid activity in the whole brain was found to be 38.1±2.3% in a group of 20 rats receiving EA for 30 min, which was 33% (p<0.01) higher than that in the control rats (28.6±1.4%, n=25). While EA produced an average increase of TFL by 72±9% in a group of 20 rats, the effect of EA analgesia in individual rats exhibited a wide variation. Statistical analysis revealed a positive correlation between the effectiveness of EA analgesia and the increase in cerebral opioid activity (r=0.61, n=20, p<0.01), suggesting that cerebral opioids may play an important part in the mediation of EA analgesia.

In contrast to the increase in opioid activity in the brain, there was a significant decrease in the opioid activity in the pituitary (-18.3%, p<0.05). When the RRA data were correlated with the effect of EA analgesia, there appeared to be a tendency of a negative correlation (r=-0.34, n=18), with the p value barely reaching significant level. The role played by pituitary opioids in EA analgesia remain to be elucidated.
CENTRAL 5-HYDROXYTRYPTAMINE, OPIATE-LIKE SUBSTANCES (OLS) 
AND ACUPUNCTURE ANALGESIA


Research Group of Acupuncture Anesthesia 
Peking Medical College, Peking

Endogenous and Exogenous Opiate Agonists and Antagonists

Summary

The interrelationship between the cerebral 5-HT content and OLS 
activity were studied in rats and correlated with the effect of 
acupuncture analgesia (A). The 5-HT turnover was associated 
with the intensity of the analgesic effect.
content following the intraperitoneal injection of parachlorophenylalanine (pCPA), the 5-HT synthesis inhibitor or intracerebral injection of 5,6-dihydroxytryptamine (5,6-DHT), the serotonergic chemical denervator, was accompanied by a parallel decrease in the effect of AA. A significant positive correlation was found between the % change of central 5-HT (x) and the effect of AA (y, % change of pain threshold over the basal level), expressed in an equation of linear regression: 

$$y = 0.428x + 26.1 \quad (r = 0.364, n = 51, p < 0.01)$$

(2). It can be seen from the equation that the effect of electroacupuncture in rats is closely related to the cerebral 5-HT content. In addition, the effect of AA would not be totally abolished, even though central 5-HT falls to a very low level. This implies that central 5-HT is an important factor but not the sole determinant of AA.

1-2. Changes in the cerebral 5-HT content during AA: As reported previously, there was a significant rise in cerebral 5-HT content during AA in rats (3). In a recent study, we have proved further that the % increase in amplitude of central 5-HT was positively correlated with the effect of AA (4). This gives affirmative support to the important role of 5-HT in AA.

2. The interrelationship between OLS and AA

2-1. Effect of blockade of opiate receptors on AA: It has been proved separately by Mayer in human beings (5) and by Pomeranz in mice (6) and cats (7) that the effect of AA could be partially abolished by opiate receptor antagonists. We have obtained similar results in rabbits (8), implying that OLS is implicated in AA; but we failed in our experiments with the rat tail flick acupuncture analgesia model. The dose of naloxone (20 μg in 50 μl infused within 16 minutes) was certainly large enough to block the analgesic effect of morphine (10 mg/kg, sc) completely, but it failed to block AA (9). An explanation should be sought for the ineffectiveness of naloxone in rats: Whether OLS does not take its part in AA in this species, or is there any other reason?

2-2. Changes in the cerebral OLS activity during AA: Rats were given electroacupuncture for 30 minutes and then decapitated for the determination of cerebral OLS activity by radio-receptor assay. It was found that in the acupuncture group, the cerebral OLS activity rose conspicuously. The % elevation of OLS activity was positively correlated with the effect of AA (p<0.01) (10), and the result was again verified in another recent study (4). This implied that central OLS is implicated and takes an important role in AA in rats.

Aiming at a resolution for the apparent contradiction in the results of experiments in rats and rabbits, we proceeded to study the interrelationship between OLS and other neurotransmitters, taking for first priority that between OLS and 5-HT.
3. The interrelationship between 5-HT and OLS

3-1. Effect of blockade of opiate receptors on cerebral 5-HT: After the rats were given intraventricular infusion of naloxone (20 ug within 16 minutes), they were decapitated immediately for the determination of 5-HT and its metabolic end product 5-HIAA in the whole brain. The cerebral 5-HT content increased by 14% on average over the control group (p<0.01) and 5-HIAA by 16% (p<0.05). The results imply that the blockade of endogenous OLS activity brought about an acceleration in the metabolism of central 5-HT.

3-2. Effect of lowering of central 5-HT on cerebral OLS activity: The decrease in cerebral 5-HT content (x) following the administration of PCPA or 5,6-DHT was accompanied by a corresponding increase in central OLS activity (y), and a high negative correlation was found between their relative contents expressed as % of normal (r=0.74, n=50, p<0.001). The regression equation (y=164.8-0.64x) implied that a decrease in the cerebral 5-HT content effected a spontaneous increase in central OLS activity.

The existence of an intimate functional interrelationship between central 5-HT and OLS, the impairment of function in anyone of these being compensated by an automatic elevation in the other, helps to explain the following experimental phenomena:

(1) The effect of AA was not totally abolished, even though the cerebral 5-HT content was reduced to less than 20% of its normal level (cf. 1-1).

(2) Blockade of cerebral OLS activity did not attenuate the effect of AA significantly in rats (cf. 2-1).

(3) Intraventricular injection of naloxone which induced a partial blockade of the effect of AA in normal rabbits was ineffective in those in which the central 5-HT content had been elevated by the injection of pargyline (8).

4. The interrelationship between 5-HT, OLS and AA

4-1. Change in the cerebral 5-HT content and OLS activity during AA in normal rats (4): In a group of 27 rats given electroacupuncture for 30 min, the cerebral 5-HT content and OLS activity were determined simultaneously after decapitation at the end of electroacupuncture. It was found that rats with high levels of both central 5-HT content and OLS activity generally exhibit excellent analgesic effects, those with elevation of either 5-HT or OLS a moderate analgesic effect, while those with no elevation or even a reduction in both showed a poor effect. The interrelationship between central 5-HT content (%, x1), OLS activity (%, x2) and the effect of AA (% increase in pain threshold, y) can be expressed by the regression equation: y=0.64x1+0.46x2-75 (r=0.69, p<0.001).
The above equation associated with the high correlation denotes that central 5-HT and OLS are important factors determining the effect of AA, and the effect of AA is related to the joint action of these neurotransmitters. In order to ascertain the general significance of the equation, the experiment was repeated under conditions of reduced 5-HT.

4-2. The interrelationship between 5-HT, OLS and the effect of AA in PCPA-treated rats: As mentioned above, the reduction of central 5-HT content after PCPA was accompanied by a spontaneous rise in cerebral OLS activity. The trend of elevation of OLS was even more marked when electroacupuncture was given to these animals. Correlative analysis of central 5-HT content and OLS activity with the effect of AA in individual rats revealed that as much as the decrease in cerebral 5-HT had been compensated by a rise in OLS, the rats retained a firmly well effect of AA. While in those rats the cerebral OLS activity failed to make up for the loss in 5-HT, the effect of AA was almost completely abolished. The results of observation in a group of 51 rats may be expressed in a regression equation: \( y = 0.61x_1 + 0.48x_2 - 62 \) (\( r = 0.60, \ p < 0.01 \)), which was very similar to that obtained in normal rats (cf. 4-1). The consistency of the general equation under different experimental conditions may well indicate the existence of a substantial interrelationship between central 5-HT and OLS with regard to the effect of AA.

4-3. The effect of simultaneous blockade of 5-HT and OLS on AA in rats (3): Intraperitoneal injection of a small dose of PCPA (200 mg/kg) reduced the cerebral 5-HT content by 52% (\( p < 0.001 \)); at the same time, the effect of AA was reduced by 19% only (\( p > 0.05 \)). Intraventricular infusion of naloxone (20 \( \mu \)g) had no apparent effect on AA also. However the effect of AA was reduced very significantly when these two measures were given in combination (-59%, \( p < 0.005 \)). These results implied that the antagonistic effect of naloxone could have been manifested in rats in case there is a reduction in the functional activity of central 5-HT. When naloxone was given in combination with large dose of PCPA (320 mg/kg ip, plus 10 mg/kg ivt), so that both the effects of 5-HT and OLS were blocked, the effect of AA was almost totally abolished (-82%, not significantly different from the basal pain threshold).

5. Conclusion

5-1. The effect of AA in rats seems to be intimately related to the cerebral 5-HT content and OLS activity, and the extent they were mobilized in the course of acupuncture.

5-2. There seems to be an intimate interrelationship and a functionally compensatory mechanism between 5-HT and OLS in the CNS.
1 denotes the effect of these significance of reduced event of AA.

The central rise in even more relative effect of increase in retained cerebral OLS of AA was in a group of 0.46 x 2 - 62 in normal on under-ence of a th regard

on AA in CPA (200 the same (p>0.05). Effect significantly (p<0.005).

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Referenc es

The aim of this study is to clarify the role of endogenous opioid peptides (EOP) in mediating electroacupuncture analgesia (EAA).

Rats were given EA of 2, 15, and 100 Hz with increasing intensity of 1, 2, 3 V through stainless steel needles inserted into bilateral hind leg points Zusanli and Sanyinjiao. Radiant heat induced tail flick latency (TFL) was measured as nociceptive test. Naloxone (NX) was given at a dose range of 0.25-20 mg/kg, sc. Antisera raised in rabbits against met-enkephalin (MEK), leu-enkephalin (LEK), β-endorphin (BE), dynorphin A (Dyn A) and dynorphin B (Dyn B) were injected intrathecally (ith) before EA administration.

NX 1 mg/kg completely abolished the analgesic effect of 2 Hz EA, partially (55%) reversed 15 Hz EAA but had no effect on 100 Hz EAA. The doses of NX needed for 50% reversal of 2, 5, 100 Hz EAA were found to be 0.5, 1.0 and 24 mg/kg, respectively. Antibody microinjection studies revealed that EAA of 2, 15, 100 Hz were best blocked by ith injection of MEK, Dyn B and Dyn A antisera respectively, whilst LEK and BE antisera were of little effect.

Conclusions: Different kinds of EOP may be released in the spinal cord by EA stimulation of different frequencies, MEK at 2 Hz, Dyn A at 100 Hz, and a mixture of enkephalins and dynorphins at 15 Hz.

We thank Dr. A. Herz for providing BE antiserum and Dr. A. Goldstein for Dyn A and Dyn B antisera. Naloxone was a gift from Endo Laboratories.
ANALGESIA PRODUCED BY ELECTROACUPUNCTURE OF DIFFERENT FREQUENCIES ARE MEDIATED BY DIFFERENT VARIETIES OF OPIOIDS IN THE SPINAL CORD

XIE Guo-Xi, HAN Ji-Sheng

Kexue Tongbao 30(5):385-391, 1985

The involvement of endogenous opioids in the mediation of electroacupuncture (EA) analgesia has been well documented. The aim of this study was to clarify whether EA of different frequencies will release different varieties of opioid peptides in producing an analgesic effect.

Rats were prepared with intrathecal cannula made of PE 10 tubing extending from the atlanto-occipital space to the lumbar spinal cord. EA was applied at bilateral Zusanli and Sanyinjiao points, the parameters of EA being 2, 15 or 100 Hz at increasing intensity of 1-2-3V for a period of 30 min. Tail flick latency (TFL) was measured before and at 10 min intervals during the period of EA. The percentage increase of TFL over the baseline level was taken as an index of analgesia. Antiserum or normal rabbit serum (NRS) was diluted 1:5 and injected intrathecally (i.th) in a volume of 10ul 10 min prior to EA stimulation.

1. 2Hz EA: In rats receiving NRS, 2Hz EA at increasing intensities of 1-2-3V caused 54, 57 and 72% increase in TFL. This effect of EA analgesia was markedly reduced in rats receiving met-enkephalin antiserum (MEK-AS, 1:8000), the corresponding values of increase in TFL being 15, 17 and 30%, respectively (p<0.05 in all time points). No significant changes in the effect of EA analgesia were observed when antiserum against leu-enkephalin (LEK-AS, 1:6000), β-endorphin (β-EP-AS, 1:50000), dynorphin A (DYN-AAS, 1:10000) or dynorphin B (DYNB-AS, 1:15000) was injected intrathecally to the rat.

2. 15Hz EA: The effect of 15Hz EA analgesia in NRS control group was 36, 56 and 70%, respectively during 1, 2 and 3V stimulation. This effect of analgesia was significantly attenuated by the i.th injection of DYN-AAS (p<0.05) or DYNB-AS (p<0.01), and moderately affected by MEK-AS (a reduction of 47-54%, p>0.05), but not by LEK-AS or EP-AS.

3. 100Hz EA: EA of 100Hz at 1-2-3V caused increases in TFL by 35, 55 and 62%, respectively. This effect of EA analgesia was significantly attenuated by the i.th injection of DYN-AAS to a level of 28, 12 and 9%, respectively (p<0.05). Antisera against MEK, LEK, β-EP, and DYNB were without effect in this regard.
In conclusion, the analgesia produced by 2Hz EA seems to be mediated by MEK, and 100Hz EA by DYNA. Analgesia of 15Hz EA may be mediated by both MEK and dynorphins. So far as spinal cord is concerned, BEP and LEK do not seem to play a significant role in the mechanisms of EA analgesia.
NEW EVIDENCE SUPPORTING DIFFERENTIAL RELEASE OF ENKEPHALIN AND DYNORPHIN BY LOW AND HIGH FREQUENCY ELECTROACUPUNCTURE STIMULATION

FEI Hong, SUN Shao-Li, HAN Ji-Sheng

Kexue Tongbao, in press, 1987

Previous studies have shown that the increase in tail flick latency (TFL) induced by low frequency electroacupuncture (EA) stimulation on both hindlegs can be blocked by a low dose of naloxone or by intrathecal (ith) injection of antibodies against met-enkephalin (MEK), whereas high frequency EA induced analgesia can be blocked only by a high dose of naloxone or by ith injection of antibodies against dynorphin (DYN), suggesting that low and high frequency EA releases MEK and DYN respectively from spinal cord of the rat. In the present study the same issue was tested from 4 different approaches.

1. Cross tolerance between 2 and 100Hz EA analgesia: Rats were given 100Hz EA continuously for 6 hours. There was a gradual decrease in the effect of EA analgesia from 100±13% in the first hour down to 12±6% at the end of 6th hour. In these rats made tolerant to 100Hz EA, 2Hz EA was still effective in producing an analgesic effect (54±8%, p<0.01 compared to 12±6%). The reverse was also true that rats made tolerant to 2Hz EA were still effective in producing analgesia when 100Hz EA was administered. The lack of cross tolerance between 2 and 100Hz EA analgesia suggest that they are mediated by different neurochemical mechanisms.

2. Cross tolerance between 100Hz EA analgesia and dynorphin analgesia: Intrathecal injection of 2.5, 5 and 10nmol of dynorphin A(1-13) (DYN) produced an increase in TFL of 31, 62 and 135%, respectively. The analgesic effect of DYN was significantly reduced in rats made tolerant to 100Hz EA (2, 19 and 60%, respectively), but not in rats made tolerant to 2Hz EA. The results implicate dynorphin as a chemical mediator in 100Hz EA analgesia, but not in 2Hz EA effect.

3. The effect of ICI 174864 on 2Hz and 100Hz EA analgesia: ICI 174864, a specific delta opioid receptor blocker, was administered intrathecally 10 min prior to EA. The effect of 2Hz EA analgesia was dose-dependently blocked by ICI 174864 in the dose range of 1-4 nmol; whereas EA of 100Hz was not affected by this compound.

4. The effect of Mr2266 on analgesia induced by 2Hz and 100Hz EA: Mr2266 is a blocker for kappa sites with only relative specificity.
Intrathecal injection of Mr2266 was performed 10 min prior to EA. The doses needed for 50% inhibition of 2Hz and 100Hz EA analgesia were 73.2nmol and 25.5nmol, respectively, suggesting that 100Hz EA analgesia was preferentially antagonized by the kappa blocker.

The results are in line with the notion that the analgesic effect of 2Hz and 100Hz EA is mediated by enkephalin (delta agonist) and dynorphin (kappa agonist), respectively.
1/11/06

Dearest Customer,

We receive many requests for information about clinical applications of electroacupuncture. Applications for pain are a very common request.

Recently, we attended the AAMA (American Association for Medical Acupuncture) conference in Atlanta in 2005, and this updated paper was presented by JI-Sheng Han. He describes the research supporting the applications of 2/100 hz frequencies using the MIXED mode as best for pain.

Your Pantheon Research equipment specifically incorporates these frequencies, as well as a mixed mode with a three second period on each frequency. This is exactly what Han describes as being best for pain.

Also, the frequencies built into the Pantheon Research equipment are exactly at 2 and 100 Hz, so this is a completely reliable parameter in treatment.

For your convenience, we have included his paper.

Thank you again,

John Hubacher
Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies

Ji-Sheng Han

Neuroscience Research Institute, Peking University, 38 Xue Yuan Road, Beijing 100083, China

Brain functions are regulated by chemical messengers that include neurotransmitters and neuropeptides. Recent studies have shown that acupuncture or electrical stimulation in specific frequencies applied to certain body sites can facilitate the release of specific neuropeptides in the CNS, eliciting profound physiological effects and even activating self-healing mechanisms. Investigation of the conditions controlling this neurobiological reaction could have theoretical and clinical implications.

Neuropeptides play important roles in various aspects of brain function (e.g. opioid peptides in pain control [1] and neuropeptide Y (NPY) in appetite modulation [2], among others). This review discusses evidence that neuropeptides could be mobilized by peripheral electric stimulation to benefit human health.

It has been shown that physiological and pathological conditions can induce release of neuropeptides. Two well-known examples are a severe painful stimulus inducing the release of opioid peptides to ease pain, and sucking of the nipples promoting the secretion of milk. Oxytocinergic neurons fire at a very low rate, of ~1 Hz (0.1–2.6 Hz) in basal conditions, but prolonged sucking by ten or more pups can bring the firing rate up to 16–50 Hz, followed by strong milk ejection within 10–12 seconds [3]. This finding suggests that neuropeptide release could be modulated by external stimulation.

Clinically, intracranial [4] or intra-spinal [5] electrical stimulation has been used through neurosurgical procedures to provide relief for patients suffering from chronic pain, with a success rate of 50–80% after one year of treatment. This pain-relief effect could involve the release of neuropeptides [6], raising the attractive possibility that others can be mobilized by peripheral electric stimulation to benefit human health.

Frequency-dependent neuropeptide release in vitro
In isolated rat neurohypophyses, field electrical stimulation induces the release of arginine vasopressin (AVP) and oxytocin (OT) into the incubation medium. Stimulation at a frequency such as 15–30 Hz was much more effective than a lower frequency such as 2–3 Hz in triggering peptide release [7], and burst stimulation was more effective than constant-frequency stimulation [8]. Furthermore, in superfused rat spinal cord slices, the release of the neuropeptide substance P (SP) per pulse of electrical stimulation was increased by frequencies in the range of 20–50 Hz, whereas release of the small-molecule neurotransmitter 5-hydroxytryptamine (5-HT) per pulse remained constant [9]. Hokfelt proposed that peptide release requires bursting or high-frequency activities, whereas individual action potentials firing at a low frequency will not induce the release of peptides [10,11]. The facilitation of peptide release by high-frequency stimulation was considered to be due to the lengthening of the action potential duration, together with the increase in frequency, leading to an increase in Ca2+ entry and in the amount of secretion per unit of action potential [12]. This concept has been supported by more recent reports [13]. However, frequency requirement can vary for different neuropeptides. In a similar experimental setting, thyrotropin-releasing hormone (TRH) could be released by electrical stimulation at a frequency as low as 0.5 and 3 Hz [14]

Frequency-dependent release of CNS opioid peptides by peripheral electrical stimulation
Peripheral electrical stimulation can be provided via electrodes placed on the skin (transcutaneous electrical nerve stimulation, TENS) or via a probe inserted through skin into the tissue (percutaneous electrical nerve stimulation, PENS). If the point of stimulation is selected according to traditional acupuncture therapy, the process is usually called electroacupuncture (EA). In fact, the difference between PENS and EA is more hypothetical than practical. One study compared the analgesic potency and the underlying neurobiological mechanisms of EA and TENS, with the acupuncture needles or the skin electrodes placed at the same ‘acupoints’, and concluded that they operate through very similar, if not identical, mechanisms [15]. Thus, the mechanisms of the aforementioned methods of peripheral stimulation are discussed under the same heading.

To facilitate the release of opioid peptides in the CNS, one can use manual acupuncture [16] or EA [17] stimulation. The parameters of the latter can be precisely characterized. It was interesting to note that analgesia...
induced by low-frequency (4 Hz) stimulation, but not that induced by high-frequency (200 Hz) stimulation, can be reversed by low doses of the opioid antagonist naloxone [17], suggesting that low-frequency stimulation can increase the release of opioid peptides in the CNS. By changing the dose of naloxone or using various opioid receptor subtype-specific antagonists, we were able to show that analgesia induced by either low- or high-frequency stimulation are both mediated by opioid peptides [18,19]. The difference was that the former was mediated by \( \mu \) and/or \( \delta \) opioid receptors [20]. These results suggest that different kinds of opioid peptides are released under these different conditions.

Direct evidence comes from our study using radio-immunooassay of spinal perfluoranes from the rat [21], showing that 2 Hz peripheral stimulation produces a significant increase in the content of enkephalin-like immunoreactivity (IR) but not in that of dynorphin IR, whereas 100 Hz increases dynorphin IR but not enkephalin IR. In a follow-up double-blind study, in collaboration with Lars Terenius of the Karolinska Institute (Stockholm, Sweden), the results obtained in rats were fully confirmed in humans [22]. These studies suggest that (1) the principle proposed by Hokfelt in 1991 [11] might have to be revised, and (2) to support our hypothesis, more evidence, obtained using different approaches, is needed.

To test whether analgesia induced by stimulation at 2 and 100 Hz are mediated differentially in the spinal cord by enkephalin and dynorphin, respectively, we performed an antibody microinjection study. Our idea was that binding of an opioid peptide molecule to its antibody to form a large protein complex would hinder its approach to the receptor, resulting in a loss of its biological function. Indeed, intrathecal injection of enkephalin antiserum resulted in a dramatic decrease in the efficacy of 2 Hz EA analgesia. This effect of antiserum diminished as the EA frequency was increased to 128 Hz. By contrast, dynorphin antiserum produced an equally dramatic decrease in the analgesic effect produced by 128 Hz EA, but this effect diminished gradually with decreasing frequency, reaching zero at 4 Hz [23] (Fig. 1). A similar approach was used to study the possible effect of \( \beta \)-endorphin in mediating EA analgesia. Injection of \( \beta \)-endorphin antiserum into rat periaqueductal grey matter resulted in an 88% decrease of analgesia at 2 Hz EA and a 61% decrease in analgesia at 15 Hz EA, with no blockade of the analgesic effect of 100 Hz EA [24].

Another example is endomorphin, a small peptide composed of only four amino acid residues that has been recognized as an endogenous opioid peptide with highly selective affinity for the \( \mu \)-opioid receptors [25]. Antibodies against endomorphin injected into the cerebral ventricle [26] or the spinal subarachnoid space [27] dose-dependently reduced the analgesia induced by 2 Hz EA stimulation, but not that induced by 100 Hz EA stimulation. This result is very similar to that obtained with the other two agonists of \( \mu \) and \( \delta \) receptor already mentioned, enkephalin and \( \beta \)-endorphin. Taken together, these studies support the proposition that, although high-frequency stimulation is preferable for the release of many CNS peptides, it should not be taken as a gold standard in determining the parameters of electrical stimulation for activating a specific neuropeptide for either experimental or therapeutic purposes.

Putative neural pathways mediating low- and high-frequency electroacupuncture-induced analgesia

The afferent impulses induced by acupuncture have been characterized to be mainly transmitted by A\( \delta \) and A\( \delta \) fibres [28]. Wang and colleagues have conducted a series of experiments to analyze the possible neural pathways responsible for the frequency-specific release of different kinds of opioid peptides in rat CNS [28] (Fig. 2). Lesion of the arcuate nuclei of the hypothalamus abolished analgesia induced by low-frequency EA but not that induced by high-frequency EA, whereas selective lesion of the parabrachial nuclei of the brainstem attenuated the effects of high-frequency EA but not those of low-frequency EA. The periaqueductal grey matter is a common element for both of the descending pain inhibitory systems. These findings have been partially supported by subsequent morphological studies using \( \text{fos} \) gene expression as marker of brain activation in the rat [30], and functional magnetic resonance imaging (fMRI) study in human volunteers (W.T. Zhang, et al., unpublished).

Optimization of peripheral electrical stimulation for maximal release of central opioid peptides

From the research already mentioned, stimulation at a single frequency, whether low or high, would not be sufficient to trigger the full release of all four kinds of opioid peptide together. To elicit the maximal release of all four, two models have been considered. Model A involves stimulation at low (2 Hz) and high (100 Hz) frequencies alternately (referred to as '2/100'), optimally spaced so that...
the residual effect produced by the low frequency stimulation could overlap with that produced by the high frequency and, therefore, elicit an synergistic effect [31]. Model B involves stimulation at 2 and 100 Hz simultaneously (referred to as '2 + 100') applied at different parts of the body, in which case all four kinds of opioid peptide might be released simultaneously (Fig. 3).

Model A has been tested carefully [32], showing that automatic shifting between low- and high-frequency stimulation for three seconds each (i.e. 2/100 stimulation) did, indeed, produce a simultaneous activation of the enkephalin and dynorphin systems, inducing a much more potent analgesic effect than that induced by a constant frequency stimulation.

For model B (2 + 100), two possibilities exist. One (B1) is that the brain is capable of clearly distinguishing two different frequencies of stimulation (2 Hz versus 100 Hz) and induces the two efferent systems to work simultaneously. The other (B2) is that two different signals (2 and 100 Hz), coming from two different sites, merge in the reticular formation of the brainstem so that they are received as a stimulation of 102 Hz, which is indistinguishable from a stimulation of 100 Hz. Model B2 is supported by at least three observations [33]. First, an increase of the content of dynorphin IR in the spinal fluid (representing an increase in release of the dynorphin peptide) was observed in both the 2/100 and 2 + 100 modes, yet an increase of the release of endomorphin IR was observed only in rats treated with 2/100 mode. Second, intrathecal injection of κ opioid-receptor antagonist norbinaltorphimide (Nob-BNI) suppressed the analgesic effect of both the 2/100 and 2 + 100 modes, whereas the μ opioid-receptor antagonist

\[ \text{D-Phe-Cys-Tyr-d-Trp-Orn-Thr-Pen-Thr} \] amide (CTOP) produced a selective blockade of the analgesia only in the 2/100 mode. Third, these results have been validated by the antibody microinjection experiment. Taken together, the 2/100 mode seems to activate both the μ/δ and κ opioid systems to induce a synergistic analgesic effect, whereas the 2 + 100 mode activates only the κ opioid system. In accordance with this hypothesis, the analgesic effect induced by 2/100 Hz was significantly stronger than that induced by 2 + 100 Hz [33]. A recent study using molecular biology has supported the concept that endogenously released dynorphin does indeed possesses a strong antinociceptive effect in the spinal cord [34].

Clinical verification of laboratory findings

The findings obtained in experimental animals have since been confirmed in humans in clinical practice. White et al.
at the University of Texas Southwestern Medical Center (TX, USA) performed a series of studies to determine whether peripheral electrical stimulation of the alternating-frequency mode would produce a significantly stronger analgesic effect than that produced by stimulation of fixed frequency in various clinical settings. Observations on the post-operative requirement of opioid analgesics [35] revealed that the alternating-mode stimulation reduced morphine requirement by 53%, whereas a constant low (2 Hz) or constant high (100 Hz) frequency produced only a 32 or 35% decrease, respectively. Ghoname et al. [36] made similar observations in patients with chronic lower-back pain and found that the alternating mode of stimulation was the most effective in decreasing pain, increasing physical activity and improving the quality of sleep (when compared with the pure low- and pure high-frequency stimulation). Because the alternating mode produced a more potent analgesic effect, it was used as a standard mode of stimulation for further studies searching for the optimal intensity [37] and optimal stimulation duration [38]. Thus, controlled clinical studies performed in the past six years using peripheral electrical stimulation for the control of various forms of acute [35,37] and chronic [36,38,39] pain have elegantly replicated what we have found in animal studies over the past two decades.

Results obtained in EA-induced analgesia have been applied to the treatment of heroin addiction with considerable success. The withdrawal syndrome observed in rats dependent on morphine can be effectively suppressed by 100 Hz EA, which accelerates the release of dynorphin in the spinal cord [40,41]. By contrast, morphine-induced conditioned-place preference (CPP), an experimental model simulating the craving of heroin addicts, can be successfully suppressed by 2 Hz EA but not 100 Hz EA [42,43]. This effect can be blocked by a small dose of naloxone, indicating the involvement of endogenous opioid peptides interacting with µ and δ opioid receptors [42,43]. As would thus be expected, in clinical practice the alternating mode of stimulation has shown strong therapeutic effects for both physical and psychological dependence in heroin addicts [44,45].

Responses of other neuropeptides to peripheral stimulation

Orphanin FQ (OFQ, also known as nociceptin) [46,47] is another opiate-related neuropeptide that modulates nociception. Recent studies describe apparent paradoxical effects of OFQ on pain modulation – analgesia in the spinal cord and pronociception (an increase in pain sensitivity) in the brain [48–52]. Analgesia induced by 100 Hz EA can be potentiated by antibodies to OFQ injected into the cerebral lateral ventricle and suppressed by the same antibodies injected into the spinal arachnoid space [53], suggesting that endogenous OFQ released by 100 Hz EA plays opposite roles in brain and spinal cord.

Cholecystokinin octapeptide (CCK-8) has been recognized as an anti-opioid peptide in the CNS [54]. The most effective method for stimulating the release of CCK-8 in the spinal cord with peripheral stimulation is to use higher frequencies (15 or 100 Hz), whereas 2 Hz is only marginally effective [55]. Liu et al. [56] measured the amount of CCK-8 in rat spinal perfusate as an indicator of CCK-8 release and found that those rats showing a significant increase in CCK release during 100 Hz EA stimulation were low responders (i.e. exhibited weak EA analgesia), whereas rats showing little increase in CCK release were high responders (i.e. exhibited strong EA analgesia). Moreover, the speed of response also plays an important role. It seems that the effect of EA analgesia is determined by, among other things, the magnitude and the rapidity of CCK release in the spinal cord in response to peripheral stimulation. This has been confirmed by the finding that a rat that is not responsive to 100 Hz EA can be transformed into a responder by injection of antisense oligonucleotides to CCK mRNA into the cerebral ventricles, which suppresses the expression of CCK in the brain [57]. Furthermore, a responder rat can be changed into a non-responder by inducing overexpression of CCK in the brain [58].

Substance P mediates nociception at the first synapse in the spinal cord. In vivo study revealed that peripheral stimulation in the 8–100 Hz range elevated the content of SP in rat spinal perfusate, with maximal effect at 15 Hz [59]. Similar results were obtained in cats (maximal release at 20 Hz) [60]. By contrast, 2 Hz peripheral stimulation produced a 50% decrease in the SP content of the spinal perfusate [59], possibly owing to the release of enkephalin [21], which in turn suppressed the release of SP [61].

Angiotensin II (AII) is another neuropeptide with anti-opioid activity [62]. The release profile is unique, with a significant decrease (+62%, P < 0.01) at 15 Hz and a significant increase (+60%, P < 0.05) at 100 Hz [63]. The decrease of AII release can be reversed by the µ-preferring opioid antagonist naloxone, which changed the 62% decrease into a 125% increase. These results suggest that opioid peptides are important modulators affecting the release of other neuropeptides: 2 Hz EA releases enkephalin, which activates AII and, thus, a negative feedback control [63]; 100 Hz EA releases dynorphin, which activates CCK-8 and, thus, another feedback control [64]. These can be considered as examples of the fine-tuning that is achieved by interactions among peptides.

Last, but not least, is the finding that brain-derived neurotrophic factor (BDNF) can be released by peripheral stimulation of 100 Hz bursts, but not by pure low- (1 Hz) or pure high-frequency stimulation (65). This has been verified in primary cultures of hippocampal neurons, in which high-frequency bursts of stimuli evoke instantaneous secretion of BDNF together with the induction of long-term potentiation (LTP) [66]. The ability of peripheral stimulation to accelerate the release of nerve growth factors has obvious clinical implications.

Concluding remarks

It has long been a dream to cure diseases by non-invasive measures that activate self-healing mechanisms, without using drugs or surgical operations. One recent effort along these lines was the use of repetitive transcranial magnetic stimulation (rTMS) to stimulate certain areas of the cerebral cortex; this has achieved limited success in the treatment of depression [67]. Evidence presented in the present
review demonstrates that it is possible to facilitate the release of certain neuropeptides in the CNS by means of peripheral electrical stimulation. In contrast to magnetic stimulation, which stimulates the superficial areas of the brain (i.e. the cortex) [67], peripheral stimulation of the skin or deeper structures activates various brain structures and/or the spinal cord via specific neural pathways (Fig. 2). Any predictions made at this stage should not be overly optimistic. But the clinical efficacy demonstrated using frequency-specific parameters to ease post-operative pain [35,37], lower-back pain [36,38] and diabetic neuropathic pain [39], and the successful application of 100 Hz (but not 2 Hz) stimulation for treating muscle spastic pain of spinal origin [68], certainly hold exciting promise for the future.

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Percutaneous Electrical Nerve Stimulation for Low Back Pain
A Randomized Crossover Study

El-sayed A. Ghoname, MD
William F. Craig, MD
Paul F. White, PhD, MD
Hesham E. Ahmed, MD
Mohamed A. Hamza, MD
Brent N. Henderson, PhD
Noor M. Gajraj, MD
Philip J. Huber, MD
Robert J. Gatchel, PhD

Context Low back pain (LBP) contributes to considerable disability and lost wages in the United States. Commonly used opioid and nonopioid analgesic drugs produce adverse effects and are of limited long-term benefit in the management of this patient population.

Objective To compare the effectiveness of a novel nonpharmacologic pain therapy, percutaneous electrical nerve stimulation (PENS), with transcutaneous electrical nerve stimulation (TENS) and flexion-extension exercise therapies in patients with long-term LBP.


Setting An ambulatory pain management center at a university medical center.

Patients Twenty-nine men and 31 women with LBP secondary to degenerative disk disease.

Interventions Four therapeutic modalities (sham-PENS, PENS, TENS, and exercise therapies) were each administered for a period of 30 minutes 3 times a week for 3 weeks.

Main Outcome Measures Pretreatment and posttreatment visual analog scale (VAS) scores for pain, physical activity, and quality of sleep; daily analgesic medication usage; a global patient assessment questionnaire; and Health Status Survey Short Form (SF-36).

Results PENS was significantly more effective in decreasing VAS pain scores after each treatment than sham-PENS, TENS, and exercise therapies (after-treatment mean ± SD VAS for pain, 3.4 ± 1.4 cm, 5.5 ± 1.9 cm, 5.6 ± 1.9 cm, and 6.4 ± 1.9 cm, respectively). The average ± SD daily oral intake of nonopioid analgesics (2.6 ± 1.4 pills per day) was decreased to 1.3 ± 1.0 pills per day with PENS (P<.008) compared with 2.5 ± 1.1, 2.2 ± 1.0, and 2.6 ± 1.2 pills per day with sham-PENS, TENS, and exercise, respectively. Compared with the other 3 modalities, 91% of the patients reported that PENS was the most effective in decreasing their LBP. The PENS therapy was also significantly more effective in improving physical activity, quality of sleep, and sense of well-being (P<.05 for each). The SF-36 survey confirmed that PENS improved posttreatment function more than sham-PENS, TENS, and exercise.

Conclusions In this sham-controlled study, PENS was more effective than TENS or exercise therapy in providing short-term pain relief and improved physical function in patients with long-term LBP.

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Author Affiliations: Eugene McDermott Center for Pain Management, Departments of Anesthesiology and Pain Management (Dr Ghoname, Craig, White, Ahmed, Hamza, and Gajraj), Surgery (Dr Huber), and Psychiatry (Drs Henderson and Gatchel), University of Texas Southwestern Medical Center, Dallas.
Percutaneous electrical nerve stimulation (PENS) is a novel analgesic therapy that combines the advantages of both TENS and electroacupuncture by using acupuncture-like needle probes positioned in the soft tissues and/or muscles to stimulate peripheral sensory nerves at the dermatomal levels corresponding to the local pathology. In a preliminary study, PENS therapy was found to be preferable to TENS and relaxation therapies in the management of pain secondary to osteoarthritis. Therefore, we designed a prospective, randomized, sham-controlled, crossover trial to compare PENS with TENS and exercise therapy in patients with long-term LBP secondary to degenerative disk disease. In addition to assessing the pain response, the patients’ physical activity, quality of sleep, sense of well-being, and oral analgesic requirements were evaluated.

METHODS

After obtaining institutional review board approval and written informed consent, 60 patients (29 men and 31 women; mean ± SD age, 43 ± 1.9 years, and weight, 66 ± 1.6 kg) with LBP secondary to radiologically confirmed degenerative disk disease were administered 4 different nonpharmacologic treatment modalities according to a randomized, sham-controlled, crossover study design. The 4 modalities consisted of sham-PENS, PENS, TENS, and flexion-extension exercise. Inclusion criteria included age older than 18 years, absence of any acute or long-term illnesses involving major organ systems, and a history of LBP, which had been maintained at a stable level with oral nonopioid analgesics for at least 3 months prior to enrollment in the study. Exclusion criteria included a history of drug or alcohol abuse, long-term use of opioid-containing medications, a change in the character or severity of the pain within the last 3 months, presence of acute nerve root irritation (sciatica), previous use of nonpharmacologic therapies (eg, acupuncture), pending medicolegal litigation (or worker’s compensation claim), or an inability to complete the health status assessment questionnaires. Patients were told that we were comparing 4 different nonpharmacologic therapies for LBP.

All patients received the 4 treatment modalities according to 1 of 4 different computer-generated sequences: (1) PENS, sham, TENS, and exercise; (2) sham, TENS, exercise, and PENS; (3) TENS, exercise, PENS, and sham; or (4) exercise, PENS, sham, and TENS. Each treatment was administered for 30 minutes 3 times a week (on Monday, Wednesday, and Friday afternoons) for 3 weeks. Upon completion of each 3-week treatment block, the patient was given 1 week off before starting the next modality. The 4 modalities were administered to all patients over the 15-week study period.

Treatment Modalities

The basic PENS therapy consisted of the placement of ten 32-gauge stainless steel acupuncture-like needle probes into the soft tissue and/or muscle in the lower back region to a 2- to 4-cm depth according to the dermatomal distribution of the pain as illustrated in part A of Figure 1. The probes were connected to 5 bipolar leads (with each lead connected to 1 positive and 1 negative probe) from an investigational (not approved by the Food and Drug Administration) low-output (<23 mA) electrical generator, which produced a unipolar square-wave pattern of electrical stimulation at a frequency of 4 Hz with a pulse width of 0.5 milliseconds. The intensity of the electrical stimulation was adjusted to produce the maximum tolerable “tapping” sensation without muscle contractions.

The sham-PENS therapy consisted of the placement of 10 acupuncture-like needle probes in an identical montage (Figure 1, A); however, no electrical stimulation was applied to the probes.

The TENS therapy consisted of the placement of 4 medium-sized (2.5-cm) cutaneous electrode pads (SnapEase, Empi, St Paul, Minn) in a standard dermatomal pattern (Figure 1, B). These electrodes were also stimulated at a frequency of 4 Hz, with a pulse duration of 0.1 milliseconds.

The lower back exercise therapy consisted of spine flexion and extension with...
the patient seated on a chair with full abduction of both hips. The patient was instructed to slowly touch the floor with both hands while remaining seated, followed by full extension of the back. This maneuver was repeated a minimum of 30 times during each 30-minute treatment session.

**Assessment Procedures**

Prior to initiating the first of the 4 treatments, patients were required to complete the Health Status Survey Short Form (SF-36). The physical component summary (PCS) and mental component summary (MCS) scores were used to assess the patient’s response to each of the therapeutic modalities. All patients were also asked to assess their baseline level of LBP, physical activity, and quality of sleep during the 48-hour interval prior to each treatment session using standard 10-cm visual analog scales (VASs), with a score of zero equalling the best to a score of 10 equalling the worst (Table 1). Repeated VAS assessments of pain, activity, and sleep were performed 3 times a week prior to each treatment session by the patient. In addition, the pain VAS was repeated immediately after completion of each treatment. The SF-36 was repeated 24 hours after completing all 9 treatment sessions with each of the 4 modalities. Patients were instructed not to change the type of nonopioid analgesic medications used during the course of the study. They were also asked to maintain a diary in which they recorded their daily usage of all analgesic medications (eg, pills per day) and any unusual reactions to the investigational therapies. Finally, each patient completed an overall assessment of the relative effectiveness of the 4 different modalities 72 hours after the last treatment session.

**Data Analysis**

The Number Cruncher Statistical System software program (version 6.0.1 for Windows, Kaysville, Utah) was used for all statistical analyses. An a priori power analysis (α, 0.05; β, 0.10; power, 90%; and SD, 2.0) determined that a group size of 60 should be adequate to demonstrate a difference of 25% between the VAS scores for the 4 modalities. The changes in the VAS scores over time were analyzed with repeated measures analysis of variance and t test, with a Bonferroni comparison test (vs control values and pairwise data), applied for multiple comparisons. Analysis of discrete (noncontinuous) data for the 4 treatment modalities was performed using the χ² test. The pretreatment and posttreatment changes and the differences between the modalities in the SF-36 scores were analyzed by paired t tests.

**RESULTS**

The pretreatment SF-36 evaluation suggested that this LBP population reported significantly lower health-related quality-of-life scores compared with the general population. The prestudy scores for this LBP population were 28.4 ± 8.4 and 40.2 ± 5.0 for the PCS and MCS, respectively, compared with general population norms of 50 for these 2 summary scores. The post-TENS treatment SF-36 scores were significantly improved over the prestudy scores for both the PCS (34.2 ± 7.4; P = .003) and MCS (42.8 ± 5.2; P = .007) components. Both TENS and sham-PENS produced small but statistically significant improvements in the PCS (29.6 ± 8.4 and 29.4 ± 8.6, respectively) and MCS (41.1 ± 5.5 and 41.0 ± 5.4, respectively) scores (P < .02). When the changes in the SF-36 scores with the PENS therapy were compared with the other 3 modalities, PENS was found to produce significantly greater improvement in posttherapy function (eg, PENS vs sham-PENS differences were +4.97 ± 2.99 and +1.84 ± 3.56 for PCS and MCS, respectively; PENS vs TENS differences were +4.66 ± 2.85 and +1.7 ± 4.19 for PCS and MCS, respectively; and PENS vs exercise differences were +5.82 ± 2.93 and +1.84 ± 3.56 for PCS and MCS, respectively).

The VAS scores for pain, physical activity, and quality of sleep prior to the first treatment session (baseline) and 24 hours after the last treatment session with each of the 4 modalities are summarized in Table 1. Compared with the baseline values, posttreatment VAS scores for pain, physical activity, and quality of sleep were improved by 46% ± 18%, 42% ± 19%, and 44% ± 20%, respectively, with PENS therapy (P < .007). TENS also produced significant decreases in the degree of pain and improvement in physical activity after 6 of 9 treatment sessions (P < .03) with an average overall improvement in the degree of pain and physical activity (from the baseline values) of 11% ± 14% and 15% ± 16%, respectively. No significant pain-relieving effects were demonstrated with either the sham-PENS or exercise therapies. Comparing the effects of the 4 treatment modalities on VAS scores for pain, physical activity, and sleep quality revealed that PENS produced significantly greater improve-

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**Table 1.** Comparison of the Average Visual Analog Scale Scores for Low Back Pain, Level of Activity, and Quality of Sleep Prior to Receiving the First Treatment and at 24 Hours After the Ninth Treatment With Each of the 4 Modalities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sham-PENS</th>
<th>PENS</th>
<th>TENS</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Degree of pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.7 (1.8)</td>
<td>6.3 (1.5)</td>
<td>6.2 (1.7)</td>
<td>6.5 (1.4)</td>
</tr>
<tr>
<td>After</td>
<td>5.5 (1.9)</td>
<td>3.4 (1.4)</td>
<td>5.6 (1.9)</td>
<td>6.4 (1.9)</td>
</tr>
<tr>
<td><strong>Level of activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.1 (2.1)</td>
<td>5.5 (2.0)</td>
<td>5.6 (2.1)</td>
<td>5.7 (1.8)</td>
</tr>
<tr>
<td>After</td>
<td>4.9 (2.1)</td>
<td>3.2 (1.7)</td>
<td>4.7 (1.9)</td>
<td>5.7 (1.8)</td>
</tr>
<tr>
<td><strong>Quality of sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>5.0 (2.3)</td>
<td>5.5 (1.9)</td>
<td>5.6 (2.1)</td>
<td>5.8 (1.9)</td>
</tr>
<tr>
<td>After</td>
<td>5.0 (2.1)</td>
<td>3.1 (1.6)</td>
<td>5.3 (2.2)</td>
<td>5.5 (1.9)</td>
</tr>
</tbody>
</table>

*Values are mean (SD) centimeters. PENS indicates percutaneous electrical nerve stimulation; TENS, transcutaneous electrical nerve stimulation.
†Significantly different from value prior to receiving the first treatment (before), P < .03, and from sham-PENS, TENS, and exercise therapies, P < .02.
‡Significantly different from value prior to receiving the first treatment (before), P < .04.
ments than sham-PENS, TENS, or exercise therapies (P<.02).

PENS produced an acute analgesic effect immediately after each treatment session (with an average 82% ± 23% decrease in the pain VAS scores vs 26% ± 19%, 9% ± 15%, and 4% ± 11% decreases with TENS, sham-PENS, and exercise, respectively). After 3 to 4 treatments with PENS, patients began reporting significant improvement in their pre-treatment VAS scores for pain, activity, and sleep compared with their baseline values (Figure 2). PENS also significantly decreased the consumption of oral...
nonopioid analgesic medication ($P<.009$) (FIGURE 3). Compared with the prestudy values, PENS therapy was associated with a 50% reduction in the daily oral analgesic requirement. In contrast, TENS therapy decreased the need for analgesic medication on only 6 days during the 3-week study period ($P<.04$). Neither sham-PENS nor exercise therapies altered the patients’ usage of their oral analgesic medication.

Finally, the overall evaluation of the 4 treatment modalities indicated that PENS was the preferred therapy in 91% of the study patients (TABLE 2). In addition, PENS was reported more effective than TENS and exercise therapies in improving the patients’ physical activity and sense of well-being. More than 80% of the patients indicated that they would be willing to pay extra money (out-of-pocket) to receive PENS therapy in the future.

**COMMENT**

This crossover, sham-controlled study demonstrated that PENS was more effective than TENS and exercise therapies in providing short-term relief of pain and in improving function in patients with stable LBP of at least 3 months’ duration. PENS was also significantly more effective than TENS and exercise therapies in reducing the need for oral analgesic medications. These findings are consistent with earlier studies by Deyo et al.¹⁹ and Marchand et al.²⁰ suggesting that TENS therapy is only marginally more effective than a placebo treatment (eg, sham-PENS) in this patient population. Of interest, Moore and Shurman.²¹ reported that combined neuromuscular electrical stimulation with TENS was significantly more effective than TENS alone in the management of long-term back pain.

PENS therapy was also highly effective in producing acute analgesia in this LBP population. More importantly, the patients began to report more sustained beneficial effects on their level of pain and physical activity, as well as their quality of sleep, after 3 to 4 PENS treatments. Due to the apparent cumulative effects of PENS over the course of the 3-week treatment period, these data would suggest that the use of this treatment modality over a longer period of time has the potential to produce prolonged beneficial effects in patients with long-term LBP. However, a more prolonged period of PENS therapy with careful follow-up at 3-, 6-, and 12-month intervals would be required to assess the long-term effects of this novel therapeutic modality in improving patient outcome.

Enhanced physical activity may be the most important outcome variable in the treatment of LBP.¹⁹,²²,²³ To achieve the maximal benefit from nonpharmacologic (so-called complementary) analgesic therapies such as PENS, it is recommended that PENS be used as part of a multimodality rehabilitation program, which also includes an ongoing exercise program. Although the simple spine flexion-extension exercise used in this investigation failed to produce a significant improvement in patient well-being when administered alone, this may be a reflection of the lack of effectiveness of this particular exercise maneuver or an inadequate period of exercising. In contrast to our findings, other investigators have found a more extensive exercise program to be as effective as TENS in reducing pain scores and disability in workers with acute LBP.²⁴ Future studies need to evaluate the effectiveness of PENS therapy in combination with a comprehensive exercise program.

The results of the SF-36 psychological assessments further support and strengthen the clinical findings by providing additional outcome measures, which demonstrates the superiority of PENS over the other...
In contrast, no signs and symptoms of the hemispheric disconnection syndrome are reported, either because they were absent or because no neuropsychological examinations were done. Thus, the MRI findings reported by Hacket et al do not explain the neurological signs and symptoms found in their patients with HACE, and it is not clear whether the MRI findings were symptomatic. Consequently, the intense T2 signals in the corpus callosum and the splenium reported by Hacket et al do not prove that HACE is related to cerebral edema.

Ralf W. Baumgartner, MD
University Hospital
Zurich, Switzerland


In Reply: We entirely agree with Dr Basnyat that HACE is a clinical diagnosis generally not requiring MRI, which is expensive and often unavailable. Magnetic resonance imaging may be helpful, however, when the diagnosis is unclear. The purpose of our study was to use MRI to understand the pathophysiology, not to advocate MRI as essential for diagnosis.

The findings published by Dr Surks 33 years ago have been confirmed in many subsequent studies. The mechanism of this shift of fluid from the vascular space on ascent to high altitude and the exact division of the fluid between the intracellular and interstitial spaces are not as clear. Nor is it known whether the brain participates in this fluid translocation to the same extent as other tissues. The studies done by Surks et al were in persons without altitude illness. In those who are ill with acute mountain sickness, a net fluid retention or antiurea also takes place, which would aggravate any fluid shift into the brain that might be taking place and contribute to cerebral edema. However, the fluid shift from the vascular space does not, in itself, provide a clue as to whether and to what extent the brain is involved, and as to whether the brain edema is cytotoxic (intracellular) or vasogenic (blood-brain barrier leak of proteins and water).

We disagree with Dr Baumgartner that the absence of a hemispheric disconnection syndrome is evidence against a vasogenic edema. The 2 are unrelated. We are well aware of the disconnection syndrome and since discovering the finding of splenial edema, we have been looking for it. However, our patients are in no condition for such testing while acutely ill; many are unconscious. Recently, our colleague Dr Ron Kramer of Denver, Colo, examined a patient with HACE (and high-altitude pulmonary edema) 10 days after the acute illness, when the brain MRI showed splenial edema, and found no evidence of a disconnection syndrome. Sophisticated testing earlier in the course of the illness is necessary before concluding the disconnection syndrome is not present to some degree. It should not be surprising, however, that involvement of a small portion of the corpus callosum with reversible edema (as opposed to stroke, for example) may not be reflected in a disconnection syndrome. We think that the symptoms of HACE are due to intracranial pressure increase, for which there is much clinical and autopsy evidence. The cause of death is brain herniation. We did not mean to imply that HACE is due to corpus callosum dysfunction. The reversible high T2 signal in the white matter is indicative of vasogenic edema in HACE.

Peter Hackett, MD
St Mary's Hospital
Grand Junction, Colo
Phil Yarnell, MD
University of Colorado School of Medicine
Denver

Informing Patients About Urinary Incontinence

To the Editor: In the December 16, 1998, issue, JAMA published an excellent Patient Page on urinary incontinence.1 Almost simultaneously, the American Urological Association (AUA) was launching a comprehensive long-term public awareness campaign on female incontinence.

One of the biggest problems about female incontinence is that so many women fail to seek treatment—either because of embarrassment or because they mistakenly believe that effective treatment modalities do not exist. To address this situation, the AUA developed and initiated its public awareness effort.

As part of the campaign, the AUA has developed 2 information sources for the general public: a toll-free telephone number (1-800-DRYLIFE) and an incontinence Web site (www.drylife.org). We invite physicians to refer female patients with incontinence problems to these resources.

Roy J. Correa, Jr, MD
American Urological Association, Inc
Baltimore, Md

In Reply: We are pleased to learn about the new public awareness campaign on urinary incontinence sponsored by the AUA and the American Foundation for Urologic Disease. We hope that these new information sources, along with the JAMA Patient Page on this topic, will help increase public awareness of potential treatments for this common problem.

Richard M. Glass, MD
Mi Young Hwang, MSJ
JAMA

CORRECTION

Incomplete Financial Disclosure and Incorrect Numbers: In the Preliminary Communication entitled "Percutaneous Electrical Nerve Stimulation for Low Back Pain: A Randomized Crossover Study," published in the March 3, 1999, issue of the Journal (1999;281:818-823), a potential financial conflict was not revealed. One month after submission of their manuscript to JAMA, Drs White and Craig incorporated a company named PENS Inc to produce a Food and Drug Administration–approvable stimulating unit to provide percutaneous electrical nerve stimulation (PENS) therapy. Drs White and Craig completed their financial disclosure statements at the time of submission but these disclosure statements were not updated after the company was incorporated.

Also, on page 819, under the heading "Methods," "mean ± SD age, 43 ± 1.9 years, and weight, 66 ± 1.6 kg" should have read 43 ± 19 years and 66 ± 16 kg.
Treatment of Substance Addiction With Acupuncture

D.E. Kendall, O.M.D., Ph.D., L.Ac
6105 Lake Lindero Drive
Agoura Hills, California 91301, U.S.A.

Abstract: Acupuncture been applied to treat drug addiction since 1972 when H.L. Wen (Wen and Hueng, 1975) first observed that electroacupuncture could relieve the symptoms of heroin withdrawal. This initiated several investigations into using acupuncture to alleviate the symptoms of abstinence syndrome brought on by acute withdrawal of drugs. Only moderate success was obtained from some of these initial explorations and treatment approaches were not consistent from study to study. These early efforts were carefully analyzed to determine what factors including point selection, duration of treatment number and spacing of treatments, stimulation frequency (Hz.), etc., that resulted in a more reliable outcome. Based on this information and considering the characteristics of the metabolic detoxification of each particular substance, protocols were devised that resulted in a rational and consistent clinical approach in treating drug addiction. These are described below for several different drugs and nicotine.

More than 2000 individuals were treated from 1981 through 1985, for a variety of substances which mostly involved nicotine (smoking) but also included marijuana, cocaine, alcohol, heroine, methadone and other opiates. An extremely high initial success rate (95-98%), which was taken as complete detoxification without any use of the substance, was achieved for all drugs. Follow up after one year showed excellent results (65-80%) for all substances. The recidivism was higher for heroin and methadone users that had been successfully detoxified and it seems that it was very difficult for some of them to break away from their previous life styles and sociological situations. They also seemed not to handle subsequent stress episodes well. This clinical effort was not originally designed as a controlled study since the most important goal was to develop repeatable and consistent treatment protocols.

The detoxification success rate of the above effort is considered accurate, even though not verified by urine or other tests. Recidivism data, however, was not rigorous. Determination of accurate recidivism was difficult because the clinic trials were not set up to efficiently obtain follow up information. Not all persons that were treated could be located and some showed a slight resentment about being checked on even though they were still drug or nicotine free. There is need for more and better controlled studies that are designed to account for the problem of obtaining accurate follow up information.

Post treatment support is extremely important and where individuals could be given or taught successful coping strategies to deal with future stress exposure or physical memory related to drug use, especially in smokers, they did better. Some patients were taught active and passive relaxation techniques and all were advised to immediately seek treatment if uncontrollable urges or events were causing them to again consider smoking or drug use. They were also advised that if they inadvertently smoked or used drugs or if they were coerced or badgered into using drugs or tobacco again, to immediately come in for treatment to avoid setting up long term addiction. Those that came in for occasional unscheduled follow up or support usually only required one treatment to get through the problem period. Some patients scheduled regular follow up or maintenance treatments every six months just to make sure they did not get any urges to relapse into drug or
nicotine use. This is one of the truly important and unique features of acupuncture therapy in that it can be easily and immediately applied in almost any circumstance. The other important feature in using acupuncture to treat addictions is that many people have tried every program available in an attempt to get off drugs, alcohol or to stop smoking without any success. Since acupuncture therapy is mainly directed toward restoring disrupted neurochemical balance brought on by addiction and subsequent abstinence, it has been very effective.

The treatment philosophy described below represents one particular approach and it is geared to outpatient consideration although the procedures work just as effective on an inpatient basis. Treatment protocols were developed to obtain the most successful, predictable and consistent results. Mild electroacupuncture stimulation is applied to some of the acupoints and this requires that the practitioner be properly trained in its use as well as in use of acupuncture itself. A trained professional acupuncturist should always be employed whenever acupuncture therapy is applied for the treatment of any condition. Less formal procedures have been applied by some groups that do not utilize electroacupuncture and they also report good results, however, statistical and follow up data was not provided in the early studies (Smith, 1979; Shakur and Smith, 1979; Smith et al, 1982, 1984) although more recent information involving crack cocaine is showing great promise (Smith, 1988).

It is generally recognized that outpatient treatment for the hard drugs has a much lower chance for success since the subject can have ready access to drugs. This is complicated by the fact that the drug supplier may not want to lose a client and therefore encourages the user to take the easy way out to avoid withdrawal and return to drugs or at least try it one more time. The other problem is the ever present peer pressure. A mistaken thought is that peer pressure is operative only in the young and impressionable; however, it appears that it is a strong factor in adults of all ages as well. Many failures to stay off even cigarettes can be directly traced to an active smoking family member or friend that encourages the person to smoke again because they are possibly threatened by the fact that the other person is trying to get off nicotine. The seriousness of this problem was illustrated by Man and Chuang (1980) who observed, in a methadone detoxification study involving 35 patients over a 6 month follow-up period, that there was an 82.9 % incidence of illegal drug use as verified by urine tests.

Despite the availability of drugs, nicotine and alcohol, many people have been successful in getting off these substances with acupuncture on an outpatient basis. If people voluntarily want to abstain from an addictive substance the chances for success are probably higher than for those subjects that are coerced or forced to withdraw due to family or legal pressure. Strong individual motivation undoubtedly contributes to the long term success after the initial detoxification although acupuncture has been successful in subjects that were unsure of their desire to quit using a particular substance. Health status or physical situation, such as being pregnant, can also provide inspiration to abstain from a drug after getting through the initial detoxification. Elderly patients that had been hospitalized with serious illnesses involving the lung and heart, for example, had a very high rate of success in nicotine withdrawal (Zalesskly, et al, 1983).

Background

There is little question that drug and substance abuse is perhaps the single most significant health hazard facing the world population today. Nicotine use alone in the United States may be directly related to at least 600,000 premature deaths each year. Although much attention is now being focused on this serious problem, drug abuse has been a major concern to the medical establishment for more than 100 years (Cowart, 1986a). Fortunately, early recognition of the potential for widespread addiction of the public to opiates and other drugs was influential in restricting their use in prescription and patent medicine (Simmons, 1906). It is estimated that before the FDA regulations to ban the use of opiates that perhaps one in every 400 Americans were already addicted to their use (Musto, 1973). Narcotic laws to enforce the ban were effective and by the 1930s there was a ten fold reduction in the number of people addicted to opiates.
The latest concern is the uncontrolled illegal importation and widespread use of cocaine. The addictive nature and hazards of cocaine use were also recognized long ago and FDA regulations have restricted its use in medicines as well. On the other hand, the public is apparently not aware of its risk because the illegal use of cocaine is pandemic. It is difficult to estimate how widespread it is being used but numbers range from 5.4 million Americans had tried it at least once by 1974 to 21.6 million in 1982 to approximately 25 million by 1986 (NIDA, 85:1414, 1985). It is estimated that there were 4 to 5 million regular users by 1985 (Amer. Fam. Phys. 31:173-176, 1985).

Substance abuse over the history of civilized man has been a complex problem because it is driven by strong economic factors that have even involved entire governments of some countries in the production and sale, usually to another country, of addictive products. It has led to wars between countries or wars to enforce the illegal import of the substance, such as the opium wars fought against China. Many of the armed conflicts in the world today are related to controlling the drug traffic in various parts of the world. The economic leverage of cocaine alone has also resulted in widespread corruption in many countries to subvert the legal systems designed to detect and enforce the laws against its distribution and use. The situation of cocaine today in the United States is reminiscent of the situation that existed 140 years ago in China. The British raised opium in India and illegally imported it into China and eventually enslaved an entire country for more than 100 years.

Many people have the idea that the solution to the problem is very simple, all one has to do is to tell the users to stop buying the drugs. However there are complications in this simple approach. First, once an individual is addicted to a substance they have little desire to stop its use and in fact many will do almost anything or go to any limits to obtain the drug involved. Even when they are successfully treated for the addiction of a substance they consciously return to its use for a variety of very weak reasons.

The power of drug dependence has been demonstrated in rats and monkeys that will press a lever to obtain intravenous alcohol, amphetamines, opiates or cocaine in deference to eating or drinking water. It has been demonstrated that monkeys prefer to press a lever to obtain intravenous cocaine instead of intravenous amphetamines, or food, although they may be starving or to having sex with a receptive female. If given a choice between a lever that dispenses a high dose of cocaine accompanied by a strong electric shock or a low dose with no shock they prefer the former. Monkeys will continue these behaviors until they die of convulsions or exhaustion (Bull. Narc. 36:3-14, 1986).

These forces have a continuing strong influence on individuals even though they have successfully gone through detoxification leading to eventual return to drug or nicotine use. Previously it has been estimated that the recidivism rate may be as high as 75% for all types of substances which is reached in one or two years after stopping drug use. This points out the need for continuing support and education for persons once they have been detoxed. It also seems that a crucial phase of the recovery occurs approximately six weeks after drug cessation where a strong urge, desire or curiosity to experiment with the drug or nicotine just one more time to demonstrate to the former addict that they have complete control over their problem. This is a very critical period and some refer to it as the six week wall. Patients need to be advised of the increased risk at this time so they know how to cope with the situation if it arises. For alcohol and opiates a follow up treatment should be scheduled at the sixth week.

The success of the stop smoking program conducted for many years in Bad Nauheim, Germany where they report an initial quit rate of 82.4% for 12,000 subjects with a 50.2% success after 10 years illustrates the importance of follow up support (Hammer, 1981). Although acupuncture was used as a treatment modality they approached nicotine addiction mainly as a behavior problem. The follow up included educating the subjects concerning the effect of nicotine on the body, analysis and effect of tobacco advertising, autogenic training to break body memory or conditioning due to smoking, yoga exercises, running, baths, films, slides, etc.

Strong education and awareness programs are vital to alert the public to the risks and consequences of substance abuse. The present trend toward reducing the percentage of people using nicotine is directly related to providing the public with information on the risk of smoking. This even includes the risk to non-smoking adults and children exposed to secondary cigarette, cigar and
With the deaths in 1986 of two nationally known professional athletes in separate incidents, where cocaine was apparently used for the first time, the public is just starting to realize the risks associated with this dangerous drug (Cowart, 1986b). Increased incidence of stroke and fatal heart attacks in younger people is also being observed because of cocaine's influence on raising blood pressure and damaging effects on the heart (Amer. J. Card. 57:496, 1986a: 57:1185-1186, 1986b; Arch. Pathol. Lab. Med. 110:479-484, 1986).

Another complication in treating drug dependence is that until now there has not been any effective and humane approach to help treat the withdrawal syndrome without the use of additional drugs. The proper application of modern acupuncture may be one of the few modalities that have promise of providing a potentially successful program in treating those individuals attempting to abstain from the use of drugs.

Philosophical Considerations

The main viewpoint in traditional Chinese medicine (TCM) in regard to substance abuse and addiction is that it is essentially a physiological problem which then can have psychological consequences. This is borne out by the knowledge that almost all smokers (nicotine addicts) started using tobacco when they were children experimenting with the forbidden fruits of adults. They really did not have any underlying psychological problems that drove them to nicotine. The same applies to alcohol as well since almost all drinkers got their start when they were young teenagers. One recent finding, however, showed that 50% of young alcoholics came from families with two alcoholic parents and another 25% had one alcoholic parent. This possibly indicates the importance of family influence on the behavior on their children.

It has been noted by Gawin and Kleber (1985) that although the presence of affective behavior problems may increase an individual's potential for drug use, 50 to 70% of abusers do not have psychiatric diagnoses. Peer pressure and the promise of euphoric bliss or group acceptance are probably the most important factors to induce individuals to try drugs for the first time. Most who tried were not aware of the addictive powers of the substance involved and physiological habituation occurred before they knew what was happening. If the substance is withheld after this point then abstinence or withdrawal syndrome becomes apparent. The subject then has to continue using the substance just to avoid the misery of withdrawal symptoms. It is also possible that some people continue the use of drugs just to once again achieve that first euphoric high only to find out that it cannot be re-experienced. This is because the most significant influence on central neurotransmitter production that produces the "high" occurs during the initial habituation phase. Once dependence is achieved the affected neurons are inhibited and additional drug intake only maintains the habituation and the state of tolerance is established.

One of the major differences in treating addictions by a primarily physiological approach, such as acupuncture, is dealing with the nomenclature or classification of the disorder. Labels such as "incurable disease" have been popularized, especially associated with alcoholism, presumably to allow the public to get the idea that it is only a case of happenstance or perhaps genetics that one individual is or is not afflicted. This classification scenario developed on the thought that if one has an incurable disease then it is okay to have it treated. The downside problem with this approach is that an individual's self esteem is damaged by being stuck with the label of "incurable" or worse yet "bad genes".

Some experts point out that substance abuse must be an incurable disease since whenever a former user of some substance tries it again they are immediately re-addicted. As it turns out this is also true if anyone including naive subjects uses almost any addictive substance, they will become addicted. Therefore any successful approach requires that the recovered addict abstain from any use of the particular substance in order to remain addiction free.

Since the addicted state causes a wide range of possible aberrant behavior, perhaps dependent somewhat on the particular drug involved, then heavy psycho-sociological counseling has usually been included in the former treatment approaches. Often this has included several weeks of
hospitalization and the use of other drugs to treat the withdrawal syndrome. The experience in using acupuncture indicates that once an individual is successfully detoxified that most of the affective behavior disorders significantly decrease or disappear. Remaining problems may then also be treatable with acupuncture. Some percentage of individuals, especially younger people, may need to be referred to counseling to resolve remaining deep-seated problems.

The treatment of substance abuse with the utilization of acupuncture is based on the fact that all animals, including humans, are addictable to many natural and artificial chemical substances. The addiction or habituation process occurs because of the effect that these substances have on certain brain centers and peripheral tissue. It is entirely independent of any weakness or propensity toward development of addiction. So the concept of disease and especially incurable disease is not involved. It is true that whenever a former addict uses a particular substance again they will more than likely become re-addicted just as they did the first time they were involved with that substance. Re-addiction occurs easier probably because of the physical memory that persists as result of conditioning neuronal circuits during the previous habituated state. This may be one of the underlying factors related to the high rate of recidivism.

Addiction Model

The application of acupuncture to treat drug use is based on a neurochemical receptor hypothesis for drug, nicotine and alcohol addiction (See, Ramsey, 1977; Stinnett, 1977; Snyder, 1980; Gillman and Lichtigfeld, 1983). The particular model as illustrated in Figure 1. considers the central system neurochemical and neuroactive make-up to be broadly classified into two categories. The first (Group A) mediate activities characterized by sympathetic outflow which includes increased heart rate, higher blood pressure, inhibition of the gastrointestinal system, decreased lacrimation and salivation as well as many other functions. These basically are all the responses to stress stimuli. Group B on the other hand are those that predominate during parasympathetic activity including lowering heart rate and blood pressure, activating the gastrointestinal system, increasing salivation and lacrimation plus other activities. These are opposite to the stress reaction and are typical in relaxation, meditation and sleep. In TCM terms Group A would be classed as Yang and Group B as Yin. Homeostatic balance occurs when these two groups of neurochemicals, yin and yang, are in equilibrium at their normal levels (See Figure 1.a).
The initial response to drug use in an inexperienced or naive individual is characterized by a marked increase of the Group A (Yang) central transmitters along with a significant elevation of the Group B (Yin) substances (See Figure 1.b). It can produce euphoria, a rush or the so-called initial high. The response can be so extraordinary that nausea, vomiting, dizziness and even unconsciousness can also result. This is very often experienced with the first time use of opiates and alcohol as well as tobacco products. It is also now understood that the induced imbalance due to many drugs, especially opiates and cocaine, is so significant that death can also be a consequence of first time use.

Support for the supposition concerning over stimulation or production of transmitters is provided by the observation that acute administration of opiates depletes CNS levels of norepinephrine (NE) and dopamine (DA). However, this effect can not be induced in tolerant animals. Also, the development of tolerance can be blocked in some animals by inhibiting the synthesis of NE which also can decrease withdrawal or abstinence syndrome.

Apparently cocaine also has a pronounced initial effect on the Group A transmitters mainly involving dopamine which could cause a significant increase in blood pressure and heart rate. This is the suspected mechanism that has resulted in stroke and heart failure in some even first time users. The net effect of these exogenous drugs is to stimulate many areas in the brain including the serotonergic nuclei of the brain stem and perhaps catecholamines involving alpha receptors. The release of catecholamines due to cocaine use could also provoke stress induced analgesia which would account for the report of total freedom of pain during the cocaine high. The other mechanism for producing analgesia could also be that cocaine activates the serotonergic and noradrenergic descending endogenous pain control system that is activated by acupuncture.

Continued use of a substance and subsequent production of central neurochemicals eventually, and often rapidly, causes habituation or tolerance resulting in the inhibition of neuronal pathways and circuits. Some substances, even including nicotine, are so potent that addiction can occur in many people with just a one time use. The habituated state is illustrated by Figure 1.c. which is mainly characterized by inhibition of certain brain nuclei and circuits that utilizes Group B transmitters. The suppression of Group B results in a relatively higher level of Group A which induces an apparent sympathetic outflow which can result in the presentation of abstinent or withdrawal syndrome. So in order to avoid the misery of withdrawal brought on by this central neurochemical imbalance, the individual needs to intake additional drugs to stimulate Group B neurochemicals in an attempt to maintain some simialnce of homeostatic balance (See Figure 1.d.). When an addicted individual stops using a particular drug that maintains the induced higher levels of Group B, the condition noted by Figure 1.c will result and the individual will experience withdrawal syndrome. This condition (Figure 1.c.) would be classed in TCM as an apparent Yang excess due to a deficiency of Yin and for this reason addiction is considered to be a Yin deficiency. The application of acupuncture reactivates the inhibited neural centers and then the individual can abstain from the drug use without experiencing withdrawal.

Tolerance and physical dependence (habituation) usually occur together but they are not necessarily identical in nature. Tolerance relates to the characteristics of the drug wherein increasing amounts are required to achieve the same physiological effect. Metabolic tolerance may also be present and it involves increased production of certain enzymes that breakdown the substance, especially in the liver, that increase in response to chronic drug, alcohol and nicotine intake. Physical dependence or habituation is the state of inhibited or depleted neural centers which produce physiological responses which are manifested as abstinence syndrome when administration of drug is discontinued or withdrawn.

Tolerance to a substance may develop without habituation, such as occurs with the chronic intake of large doses of a vitamin, which does not produce abstinence syndrome when withdrawn. Likewise habituation may occur with a single dose of a drug, such as methadone, which will produce abstinence syndrome but tolerance is not yet established. For all major drugs, alcohol and nicotine theses differences associated with habitation and tolerance cannot be separated.
Mechanisms of Acupuncture in Treating Addictions

The discovery that electroacupuncture could relieve the symptoms of heroin withdrawal (Wen and Cheung, 1975) occurred at about the same time that studies were being performed to comprehend the physiological mechanisms of acupuncture mostly related to analgesia. There are many common pathways between the endogenous pain controlling systems and those which respond to drug, nicotine and alcohol use. Even though some drugs such as amphetamines, cocaine and nicotine are considered stimulants and others are depressants, such as alcohol and opiates, they all have profound influence on the production of catecholamines, serotonin and endogenous opiates. Each addictive substance may primarily affect only one particular central transmitter or neurochemical but most of these have functional interrelationships. Consequently there are general responses in the addictive process involving many common substances.

There is a correlation between the pharmacological agents that stimulate central neurochemicals to produce physical dependence and tolerance and the central processes that are activated by acupuncture. Just as overstimulation of these central nuclei by exogenous substances cause habituation, long duration (several hours) or repeated application of electroacupuncture stimulation can also produce tolerance. This tolerance shows cross tolerance with morphine (Han and Tang, 1981; Zhou, et al, 1985; Han, et al, 1985; Tang, et al, 1985). serotonin (Li, et al, 1982, 1985) and norepinephrine (Xie, et al, 1984; Xie, et al, 1985). Once electroacupuncture tolerance is achieved further stimulation will fail to produce significant analgesia. Acupuncture stimulation, however, does not produce physical dependence. Cheng, Pomeranz and Yu (1980), however, observed that electroacupuncture treatment of morphine dependent mice reduced signs of withdrawal, without showing cross tolerance.

Common pathways are also demonstrated by the fact that certain pharmacological agents can either enhance acupuncture analgesia or cause it to be attenuated (Han, et al, 1980; Han and Terenius, 1982). Many of these same agents can influence abstinence syndrome with an increase of acute symptoms correlating with attenuation of acupuncture analgesia (AA) and a decrease associated with the augmentation of (AA). The opiate antagonist naloxone, for example, can produce immediate presentation of abstinence syndrome in a chronic heroin user. Naloxone also blocks the analgesia produced by acupuncture stimulation (Mayer, 1977; Chapman, 1977; Malizia, 1978). Acupuncture analgesia is also attenuated by an influence on central catecholamines involving alpha receptors. GABA and cAMP (See Table 1, left hand column) and is augmented by serotonin, endogenous opiates, acetylcholine, prostaglandin E and cGMP (See Table 1, right hand column). These would correspond to Group A and B respectively noted in Figure 1. The main central neurochemicals or neurotransmitters involved that are jointly influenced by drug use and acupuncture stimulation are as follows:

Serotonin (5-Hydroxytryptamine, 5HT)

Central serotonin may be most important in the final pathway involved both in the mediation of acupuncture analgesia and the physiological effects of drugs and subsequent development of habituation and tolerance. Acupuncture induced analgesia and acute administration of morphine both cause an increased release of brain 5HT (Yi, et al, 1977). Liang, et al (1981), also observed that the individual variations in acupuncture analgesia in rat was directly related to brain levels of endogenous opiates and serotonin. Tolerance to electroacupuncture is reversed by microinjection of 5HT into the nuclei accumbens in rabbit (Xuan, et al, 1982) and both electroacupuncture and morphine tolerance is reversed by intraventricular or intracerebral injection of 5HT (Xuan, et al, 1985) or the intraventricular injection of the 5HT precursor, 5-hydroxytryptophan (5HTP) in rat (Li, et al, 1982). Intraperitoneal injection of 5HTP also produces tolerance that shows a cross tolerance with electroacupuncture analgesia and morphine (Li, et al, 1985).

Endogenous Opiates

It is quite obvious that the use of exogenous opiates has a profound influence on endogenous opiate receptors. Naloxone, an opiate receptor blocker, can bring on abrupt withdrawal syndrome in heroin addicts and in morphine dependent rats (Lorenz, et al, 1975). It can also block or attenuate the analgesia produced by electrical stimulation or electroacupuncture (Mayer, 1977; Chapman, 1977) in
human subjects and animals as well. Naloxone administered after acupuncture therapy could cancel the beneficial effect of reducing withdrawal symptoms in nicotine, marijuana and alcohol users (Malizia, 1978). However, abstinence syndrome can be repressed in opiate dependent animals (Lorenz, et al, 1975; Wen, et al, 1979) and human subjects (Wen, 1977), given naloxone prior to acupuncture treatment. Wen (1977) successfully used this approach to produce rapid detoxification in heroin addicts using only a single electroacupuncture treatment of 3 to 4 hours duration in combination with pre-administration of naloxone.

The met-enkephalin levels in the cerebral spinal fluid (CSF) of heroin addicts was observed to increase by electroacupuncture (Wen, 1980; 1983) although plasma and CSF levels of beta-endorphin did not change (Wen, et al, 1980). However, beta-endorphin activity in the brain did increase in morphine dependent mice treated for naloxone induced withdrawal using electroacupuncture (Wen, et al, 1979). Inhibitors of the enzymes that breakdown endogenous opiates can potentiate the effect of electroacupuncture indicating a common path between receptors stimulated by opiates and acupuncture.

**Norepinephrine (NE)**

Acupuncture analgesia is also attenuated by an influence on central catecholamines involving alpha receptors (Xie, et al, 1983; Xie, et al, 1985). One of the important actions of cocaine is the ability to block the re-uptake of norepinephrine with the consequence of increasing its level and enhancing the effect on the sympathetic system. This may be very significant in relationship to cocaine's damaging potential to the heart and blood vessels.

Lorenz, et al (1975) observed that plasma catecholamine levels were significantly decreased in morphine dependent rats treated with electroacupuncture for naloxone induced withdrawal.

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<thead>
<tr>
<th>ATTENUATES AA</th>
<th>AUGMENTS AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease 5HT by Cinanserin, PCPA, PCA or 5,6,DHT.</td>
<td>Increase 5HT With Pargyline or Clomipramine.</td>
</tr>
<tr>
<td>Tolerance or Depletion of 5HT by Repeated Electro Acupuncture.</td>
<td>Increase 5HT with 5HTP.</td>
</tr>
<tr>
<td>Block Opiate Receptors By Naloxone.</td>
<td>Increase OLS with Bacitracin, D-Phenylalanine or D-Leucine.</td>
</tr>
<tr>
<td>Production of Possible AOS by Repeated Electro Acupuncture.</td>
<td>Inhibit Enkephalinase with Thiorphan, Captopril or Bestatin.</td>
</tr>
<tr>
<td>Blockade of ACh Synthesis with Hemicholine (HC-3).</td>
<td>Increase in ACh by Physostigmine, Neostigmine or Eserine.</td>
</tr>
<tr>
<td>Stimulate DA or Alpha-Receptors with L-DOPA, Apomorphine or Clonidine.</td>
<td>Block DA Receptors by Droperidol, Spiroperidol or Haloperidol.</td>
</tr>
<tr>
<td>Increase Central NE With DOPS.</td>
<td>Destroy Ascending NE Fibers by 6-OHDA.</td>
</tr>
<tr>
<td>Block Beta-Receptors with Propanolol.</td>
<td>Block Alpha-Receptors with Phentolamine.</td>
</tr>
<tr>
<td>Inhibit Synthesis of PDE With Aminophyline.</td>
<td>Increase Synthesis of PDE With Imidazole.</td>
</tr>
<tr>
<td>Increase Central cAMP.</td>
<td>Increase Central cGMP.</td>
</tr>
<tr>
<td>Decrease PGE with Paracetamol.</td>
<td>Increase Prostaglandin E (PGE) by ICV Injection.</td>
</tr>
</tbody>
</table>

Dopamine (DA)

Primarily concentrated in the corpus striatum or basal ganglia system of the brain, this transmitter forms an important feedback control circuit from the substantia nigra (SN) to the dorsal raphe nuclei (NDR). The NDR in turn supplies the SN with 5HT containing neurons. It is thought that the action of cocaine is principally mediated by its affect on DA receptors but its influence on blocking the re-uptake of norepinephrine as noted above may also be of prime importance. Acute injection of morphine will initially increase the synthesis of DA in the rat brain which then produces tolerance to this effect thereby decreasing DA. Opiate abstinence is then associated with an increased synthesis of DA in the CNS and antagonists of DA can exacerbate certain withdrawal responses to morphine. The acute effects of morphine can also be antagonized by DA antagonists probably by accelerating the development of tolerance through the increased levels of DA (See Ramsey, 1977). Antagonist to DA, such as haloperidol, has been shown in a dose dependent manner to block signs of abstinence syndrome of opiates. Acupuncture induced analgesia is also enhanced by the DA antagonists, droperidol, spiroperidol and haloperidol and is attenuated by the agonists L-DOPA, apomorphine and clonidine.

Effectiveness of Acupuncture In Treating Addictions

Abstinence syndrome is characterized by increased metabolism of the different neurotransmitters noted above which are normalized as result of acupuncture stimulation (Sytinsky and Galebslaya, 1981). Homeostatic or corrective mechanisms that are disturbed usually show a phase of unbalanced elevation of sympatico-adrenal activity. Stimulation of the central catecholamine receptors is probably the most important biochemical mechanism responsible for the disturbance of the vegetative organ functions under abstinence. Plasma levels of catecholamines (Lorenz, et al, 1975), adrenocorticotropic hormone (ACTH) and cortisol (Wen, et al, 1978) and thyroid stimulating hormone (TSH) (Wen, et al, 1980) have been observed to increase in opiate dependent animal and human subjects during withdrawal syndrome. These levels are shown to decrease along with a corresponding decrease in abstinence symptoms as result of electroacupuncture. A decrease was not observed in non-addicts that were treated. Once detoxification is achieved and withdrawal symptoms are not apparent then electroacupuncture does not produce any further reduction in these parameters.

These studies correlate with the effect that mild electroacupuncture stimulation has on inhibiting sympathetic nervous system outflow (Cao, et al, 1983). Strong electroacupuncture stimulation however produces sympathetic activation indicating that it can induce a stress type reaction. This finding is consistent with several other studies that have shown that strong stimulation can produce stress. Impaired or habituated neuronal circuits or nuclei are basically reactivated by acupuncture stimulation to restore vegetative organ functions that are disturbed in the process of withdrawal syndrome.

The application of acupuncture may be one of the most viable approaches to successfully treating drug and substance addiction. Wen and Teo (1975) for example found that electroacupuncture was twice as effective as methadone in detoxifying heroin addicts. The obvious advantage of acupuncture over using methadone is that the subject is not addicted to another drug to replace the original drug. Many of the early studies achieved poor or confused results (See Tables 2,3,4 and 5) as might be expected in any early research effort because there were considerable variations in the treatment approaches. This included differences in the application of points, duration and number of treatments, frequency of electrostimulation, use of adjuvant drugs, inpatient or outpatient basis and some with or without electrostimulation. Also the criteria of success were varied with some studies taking into account reduction in substance use as a measure of success. Several studies failed to provide any measure of success or perform any follow-up assessment and so these can only be considered as philosophical methodology. Almost all of the studies to date suffer from lack of accurate follow up information perhaps because the difficulty in this task was not properly thought out before the study was undertaken. Despite many of these differences a high percentage of success in some studies indicates perhaps properly applied acupuncture can be a very useful modality in treating drug use. Schwartz (1988) however, reviewed much of this data and concluded that acupuncture is not particularly effective in treating smoking and Crottraux, et al(1983) in a controlled study determined that acupuncture although initially
better was only as good as placebo in the long run. The important question is to determine which of any of the factors in these studies were most significant in leading to a high degree of success so that these can be used to design improved and more successful treatment protocol.

Most early studies that relied on press needles, a small wire thumb tack device which is stuck into points on the auricle, or surgical staples were generally ineffective (Tennant, 1976; Gilby, 1977; Parker and Mok, 1977; Sun, 1982; Fang, 1984). When considering the risk of serious infection due to long duration insertion of these devices (5-10 days) their use for any ailment is questionable. Some researchers that did get significant results using press needles or surgical staples also used other body needle treatments and some with electrical stimulation (Sacks, 1975; Wu, 1980; Kusumi, 1986). Point selections in some studies were poor and when attempting to compare so-called sham and real points or whether the treatment was influenced by expectation, not sufficient information was derived to make accurate determination (Steiner, et al, 1982; Lamontagne and Annable, 1979), Studies that used the "Lung Point" on the ear or locations near the ear got consistently better results probably because they stimulated a branch of the 10th cranial or Vagus nerve (Wen and Teo, 1977; Wen, 1977; 1980; Patterson, et al, 1984), Tan, et al (1987) used laser stimulation on the Lung and Shenmen points on the ear and noted that success was a function of the power applied with 2.0 milliwatts (mW) being almost ineffective and 3.0 mW producing significant results. This is probably due to the fact that the lower power levels did not cause sufficient tissue damage to provoke the acupuncture reaction (See Kendall, 1989).

The effectiveness of ear points in comparison to wrist or nose points has also been examined (Fang, et al, 1984; Tan, et al, 1987) showing that ear points are more efficacious and highly successful results reported by Olms (1981) by using his specially named point "Tee Mee" could not be confirmed.

**Table 2. Summary of Studies Evaluating the Effectiveness of Acupuncture in Treating Nicotine Addiction.**

<table>
<thead>
<tr>
<th>No. Of Cases</th>
<th>Treatment Schedule</th>
<th>Initial Success%</th>
<th>Follow Up: Months</th>
<th>Success%</th>
<th>Point Use: Body</th>
<th>Ear</th>
<th>Freq (Hz)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>642</td>
<td>5 Times Over 2 Wks</td>
<td>6</td>
<td>60.6</td>
<td></td>
<td>P</td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>44</td>
<td>7 Days (Lu)</td>
<td>36.4</td>
<td>3</td>
<td>20.5</td>
<td>P</td>
<td></td>
<td></td>
<td>(2)</td>
</tr>
<tr>
<td>48</td>
<td>7 Days (Kid)</td>
<td>33.3</td>
<td>3</td>
<td>14.6</td>
<td>P</td>
<td></td>
<td></td>
<td>(2)</td>
</tr>
<tr>
<td>21</td>
<td>2 Times/Wk For 3 Wks</td>
<td>1.5</td>
<td>4.0</td>
<td></td>
<td>N</td>
<td></td>
<td>100/2</td>
<td>(3)</td>
</tr>
<tr>
<td>20</td>
<td>3 Weeks</td>
<td>1.5</td>
<td>28.0</td>
<td></td>
<td>P</td>
<td></td>
<td></td>
<td>(3)</td>
</tr>
<tr>
<td>50</td>
<td>2 Times in 1 Week</td>
<td>27.5</td>
<td>3</td>
<td>10.0</td>
<td>N</td>
<td></td>
<td></td>
<td>(4)</td>
</tr>
<tr>
<td>1138</td>
<td>1 Or 2 Times</td>
<td>82.0</td>
<td>3</td>
<td>56.0</td>
<td>NP</td>
<td>N</td>
<td></td>
<td>(5)</td>
</tr>
<tr>
<td>308</td>
<td>One Treatment</td>
<td>18</td>
<td>25.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6)</td>
</tr>
<tr>
<td>210</td>
<td>1, 2, Or 3 Weeks</td>
<td>91.0</td>
<td></td>
<td></td>
<td>N</td>
<td>P</td>
<td></td>
<td>(7)</td>
</tr>
<tr>
<td>535</td>
<td>One Treatment</td>
<td>84.0</td>
<td>75.0</td>
<td></td>
<td>TM</td>
<td></td>
<td></td>
<td>(8)</td>
</tr>
<tr>
<td>32</td>
<td>2 Times/Wk For 2 Wks</td>
<td>6</td>
<td>3.2</td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>(9)</td>
</tr>
<tr>
<td>31</td>
<td>10 Days (LU &amp; SM)</td>
<td>84.0</td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>(10)</td>
</tr>
<tr>
<td>194</td>
<td>3 Times</td>
<td>95.0</td>
<td>24</td>
<td>30.0</td>
<td>N</td>
<td>L</td>
<td></td>
<td>(11)</td>
</tr>
<tr>
<td>85*</td>
<td>4-8 Times In 2-4 Wks</td>
<td>71.0</td>
<td></td>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td>(12)</td>
</tr>
<tr>
<td>28</td>
<td>Real Points</td>
<td>6</td>
<td>18.0</td>
<td></td>
<td>P</td>
<td></td>
<td>Low</td>
<td>(15)</td>
</tr>
<tr>
<td>27</td>
<td>Placebo Points</td>
<td>6</td>
<td>15.0</td>
<td></td>
<td>P</td>
<td></td>
<td></td>
<td>(13)</td>
</tr>
<tr>
<td>33</td>
<td>10 Times Over 3 Wks</td>
<td>70.0</td>
<td>3-8</td>
<td>39.0</td>
<td>N</td>
<td></td>
<td></td>
<td>(14)</td>
</tr>
<tr>
<td>28</td>
<td>10 Times Over 3 Wks</td>
<td>11.0</td>
<td>3-8</td>
<td>7.0</td>
<td>N</td>
<td></td>
<td></td>
<td>(14)</td>
</tr>
<tr>
<td>26</td>
<td>5 Days NET</td>
<td>98.4</td>
<td>12</td>
<td>78.5</td>
<td></td>
<td></td>
<td></td>
<td>Low (15)</td>
</tr>
<tr>
<td>108</td>
<td>Real Points</td>
<td>12</td>
<td>43.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(16)</td>
</tr>
<tr>
<td>92</td>
<td>Placebo Points</td>
<td>12</td>
<td>21.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(16)</td>
</tr>
<tr>
<td>518</td>
<td>Once/Wk For 2-8 Wks</td>
<td>59.5</td>
<td></td>
<td></td>
<td>P</td>
<td></td>
<td>8-10</td>
<td>(17)</td>
</tr>
<tr>
<td>488</td>
<td>24 X/Wk</td>
<td>60.0</td>
<td>2-24</td>
<td>24.0</td>
<td></td>
<td></td>
<td></td>
<td>(18)</td>
</tr>
<tr>
<td>82</td>
<td>5-30 Days</td>
<td>41.5</td>
<td></td>
<td></td>
<td>P</td>
<td></td>
<td></td>
<td>(19)</td>
</tr>
<tr>
<td>26</td>
<td>3 X/Wk, 2Ws 2mW</td>
<td>15.4</td>
<td></td>
<td></td>
<td>L</td>
<td></td>
<td></td>
<td>(20)</td>
</tr>
<tr>
<td>20</td>
<td>3 X/Wk, 2Ws 2.5mW</td>
<td>40.0</td>
<td></td>
<td></td>
<td>L</td>
<td></td>
<td></td>
<td>(20)</td>
</tr>
<tr>
<td>28</td>
<td>3 X/Wk, 2Ws 3mW</td>
<td>70.4</td>
<td></td>
<td></td>
<td>L</td>
<td></td>
<td></td>
<td>(20)</td>
</tr>
</tbody>
</table>

Table 3. Summary of Studies Evaluating the Effectiveness of Acupuncture in Treating Alcoholism

<table>
<thead>
<tr>
<th>No. Of Cases</th>
<th>Treatment Schedule</th>
<th>Initial Success%</th>
<th>Follow Up: Months Success%</th>
<th>Point Use: Body Ear</th>
<th>Freq. (Hz) EA</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>5 Times Over 2 Weeks</td>
<td>60.0</td>
<td>6 31.0</td>
<td>N S Low</td>
<td>125</td>
<td>(21)</td>
</tr>
<tr>
<td>10</td>
<td>3 Times/Day for 3 Days, 1 Time/Day for 2 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>190</td>
<td>4 times 1st Week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 6 Times in 3 Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Varied</td>
<td>97.0</td>
<td>5-6 79.0</td>
<td>N N</td>
<td></td>
<td>(24)</td>
</tr>
<tr>
<td>23</td>
<td>10 Days NET</td>
<td>98.4</td>
<td>12 78.5</td>
<td></td>
<td>Low</td>
<td>(15)</td>
</tr>
<tr>
<td>27</td>
<td>5 Days</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td>3 Times/Wk for 28 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Times/Wk for 42 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow Up: Months Success%

- 31.0
- 25.6
- 24.4

N: Needle; S: Staple puncture; D: Adjuvant Drug; NET: Neuroelectric Therapy; EA: Electroacupuncture.


Table 4. Summary of Studies Evaluating the Effectiveness of Acupuncture in Treating Opiate and Other Drug Addiction

<table>
<thead>
<tr>
<th>No. Of Cases</th>
<th>Treatment Schedule</th>
<th>Initial Success%</th>
<th>Follow Up: Months Success%</th>
<th>Point Use: Body Ear</th>
<th>Freq. (Hz) EA</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>187</td>
<td>5 Times Over 2 Weeks</td>
<td>61.0</td>
<td>12 20.0</td>
<td>N + D</td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>18</td>
<td>Staple implant</td>
<td>6.0</td>
<td></td>
<td>S</td>
<td>(28)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>55.5</td>
<td></td>
<td></td>
<td>(30)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3 Times/Day For 3 Days, 1 Time/Day For 2 Days</td>
<td>20.0</td>
<td></td>
<td>N N</td>
<td>(21)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>36.0</td>
<td>12 20.0</td>
<td>N + D</td>
<td></td>
<td>(31)</td>
</tr>
<tr>
<td>35</td>
<td>2 Times/Day For 8 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(26)</td>
</tr>
<tr>
<td>15</td>
<td>20 Treatments</td>
<td>51.4</td>
<td></td>
<td>N + D</td>
<td></td>
<td>(33)</td>
</tr>
<tr>
<td>19</td>
<td>2 Times/Day For 8 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(27)</td>
</tr>
<tr>
<td>303</td>
<td></td>
<td>52.0</td>
<td>10 5.7</td>
<td>N + D</td>
<td></td>
<td>(32)</td>
</tr>
<tr>
<td>50</td>
<td>1 Time, 3-4 Hours</td>
<td>82.0</td>
<td>12 80.3</td>
<td>N + D</td>
<td></td>
<td>(29)</td>
</tr>
<tr>
<td>300</td>
<td>1-3 Times/Day For 2 Wks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(30)</td>
</tr>
<tr>
<td>130</td>
<td>10 Days NET</td>
<td>98.4</td>
<td>12 80.3</td>
<td></td>
<td>Low</td>
<td>(15)</td>
</tr>
<tr>
<td>14</td>
<td>2 to 7 Days</td>
<td>85.7</td>
<td></td>
<td></td>
<td></td>
<td>(34)</td>
</tr>
</tbody>
</table>

N: Needle; S: Staple puncture; NET: Neuroelectric Therapy; D: Adjuvant Drug; EA: Electroacupuncture.


Table 5. Summary of Studies Evaluating the Effectiveness of Acupuncture in Treating Cocaine Addiction

<table>
<thead>
<tr>
<th>No. Of Cases</th>
<th>Treatment Schedule</th>
<th>Initial Success%</th>
<th>Follow Up: Months Success %</th>
<th>Point Use: Body Ear</th>
<th>Freq. (Hz) EA</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 Times/Day For 3 Days, 1 Time/Day For 2 Days</td>
<td>100.0</td>
<td></td>
<td>N N</td>
<td>125</td>
<td>(21)</td>
</tr>
<tr>
<td>5</td>
<td>2 Times/Day</td>
<td>100.0</td>
<td></td>
<td></td>
<td>0.5</td>
<td>(35)</td>
</tr>
<tr>
<td>46</td>
<td>Daily</td>
<td>52.0</td>
<td></td>
<td>N N</td>
<td></td>
<td>(36)</td>
</tr>
<tr>
<td>1500</td>
<td>Daily</td>
<td>20.0</td>
<td></td>
<td>N N</td>
<td></td>
<td>(36)</td>
</tr>
</tbody>
</table>

N: Needle; EA: Electroacupuncture.

In those studies where treatment was given on contiguous days the results were generally better. Where there was a break in the treatment, such as over a week end some subjects experienced withdrawal symptoms (Tan, et al, 1987). One interesting study conducted by Bullock, et al (1987), with long term chronic alcoholics, treated the subjects in three different phases. The first phase (I) consisted of daily treatments for five days followed by phase II consisting of 3 treatments per week for four weeks und then the last phase (III) involving treatments twice a week over a 45 day period. Ten of twenty seven (37%) of a real point group made it through the treatment program whereas only two of twenty two (7.4%) of a sham point group were successful.

Other alcohol treatment studies that included the detoxification phase reported that subjects had no withdrawal symptoms (Olms, 1984; Lewenburg, 1984). Yang and Kwok (1986) found that electroacupuncture reduced withdrawal symptoms in morphine dependent rats by 85% and certain herbs were 68% effective.

**Treatment Protocol**

The information derived from the early studies was used to develop highly successful clinical procedures to treat substance addiction. The basic approach in using acupuncture considers both the disturbed vegetative functions as result of abrupt abstinence which provokes withdrawal syndrome and the metabolic detoxification processes. Withdrawal relates mainly to affected neural centers and receptors in the brain and to some extent to receptors in the gastrointestinal system. Metabolic detoxification relates mainly to liver function in breaking down various drugs and substances which are then eliminated from the body via the kidneys and bladder. The detoxification profile of a particular substance then is related to the time it takes to clear the breakdown products from the body. The work of Kao and Lu (1974) show that the frequency of withdrawal symptoms decrease with time which indicates that withdrawal correlates with the time decrease in the metabolic detoxification. The clinical approach then is to match the detoxification and withdrawal profile with the appropriate treatment schedule.

One of the main features in the treatment protocol is that the specific drug or substance is not used again (total abstinence) after the first treatment. In the case of nicotine the subjects are requested to dispose of their unused cigarettes prior to leaving the clinic. They are also asked if there are any in their automobile in which case they are requested to bring them back to the clinic for disposal after the treatment.

Acupuncture stimulation reactivates the inhibited neural centers, however, if a significant level of the substance is still present in the blood, because of the slow rate of metabolic breakdown, the effect of the treatment is transitory. This is because the affected neural areas will again be influenced by the remaining substances to cause re-inhibition which then results in the presentation of withdrawal symptoms. Therefore treatment protocol must consider the time dependent characteristics involved in how long it takes for the metabolic breakdown and clearance of the drug or substance from the body. Treatment is provided daily or more often to keep the affected neural centers reactivated over the time period it takes to eliminate all of the drug or substance.

Nicotine for example, is quickly broken down and eliminated from the body perhaps in only two to four days and a chronic user must keep smoking to maintain the critical blood nicotine level to avoid withdrawal. Some heavy users often awake in the middle of the night with a need to smoke because their blood nicotine levels become uncomfortably low while sleeping since the liver continues to breakdown the nicotine. Because nicotine is readily cleared from the body it can be treated over a relatively short time span. Other substances take a longer time to be eliminated, perhaps seven to ten days and hence the treatment period is correspondingly longer. Also, the opiates such as heroin, methadone, opium, etc, have widespread effects on the many receptors in the brain and body and consequently withdrawal symptoms can be far more severe than other substances and the frequency of treatments is increased to compensate for this aspect of the problem.

Psychological counseling is usually not involved in the treatment approach since it seems that the most important aspect of the problem is to get the user through the detoxification phase without experiencing significant withdrawal misery. Follow up treatments a few weeks after the initial detoxification seem to be important and patients should be advised to make use of local support groups.
associated with their particular problem. They also can be provided with other training and education to help cope with other physiological habits and body memory. In addition the subject is always advised to seek immediate treatment if and when uncontrollable urges or cravings for the drug or nicotine occur before the person starts using the substance again. One very critical consideration is that should an individual start smoking again or using the former drug for which they were treated and they decide to be treated once more no criticism is made because the person started using the substance again. Criticizing or blaming the person for failure only serves to attack their self esteem which is already damaged as result of substance addiction. So care is taken to maintain a positive approach in re-treating the individual.

Point Selection
The most basic acupuncture point used in the generally successful detoxification protocols involves Lung 2 located approximately in the center of the lower one third of the cavum concha of the auricle. Its importance derives from the fact that this is the only place on the superficial body where a small branch of the Vagus Nerve (10th Cranial) can be directly stimulated. Lung 1 point on the ear, which is located on the upper one third portion of the cavum concha, also has a small sprig of this nerve. However, a comparison study of almost 500 smokers treated with both Lung 11 and Lung 2 to an equal number using only Lung 2 in the point selection showed no difference in the success of the two groups. In order to minimize the total number of points required for successful treatment, only the Lung 2 location of the Vagus nerve is utilized along with other ear and body points.

Treatment success is enhanced by the application of electroacupuncture and therefore one additional point is required on the ear to provide an electrical pathway to restrict the current flow only to the area of the auricle. The point Shenmen, located at the apex of the triangular fossa, provides this feature and it is also an excellent point based on its known traditional application. Low frequency stimulation seems best which is consistent with the known frequency response of the afferent nerves and brain nuclei. Also, it has been demonstrated that frequencies above 60 to 100 Hz. can produce stress analgesia which is not a desired response in treating addictions.

Other traditional points are used such as the so called “Four Gates” consisting of bilateral use of Hegu (LI4) and Taichong (Liv3), which are located at the motor point of the first interosseous muscles of the hands and feet respectively. These points have a long traditional use in producing profound relaxation and suppression of sympathetic nervous system outflow. The traditional points noted for detoxification properties, such as Fuliu (Kid7) and Zhubin (Kid9) are also used in the case of alcohol and opiate treatment. The use of kidney points is appropriate because in Traditional Chinese Medicine (TCM) the kidneys are considered as the main organ for detoxification. The importance of the Zhubin (Kid9) probably is related to the fact that this point is coincident with the medial motor point of the soleus muscle which means its stimulation will provoke a very profound analgesia in the body since it is a large tonic muscle. Fuliu (Kid7) is located a distance of three finger breaths below point Zhubin.

In the treatment of pregnant individuals only the two points on the auricle (Lung 2 and Shenmen) are used to avoid the risk of inducing labor by using feet and leg points. In addition the point Hegu (LI4) is generally counterindicated in pregnancy. Also, in the treatment of elderly subjects the electroacupuncture tends to produce profound relaxation since most of these individuals are energy (Qi) deficient and so it is advisable to make certain that some other person brings them in for treatment. This can avoid the possible risk of the elderly person falling asleep while driving home. All the other normal restrictions related to needling also apply.

Nicotine Treatment Protocol
The treatment for nicotine addiction and marijuana usually only requires two days, with one treatment each day because of their quick metabolic detoxification profile (See Figure 2). The withdrawal symptoms are greatest a few hours after abstaining from smoking when the plasma nicotine starts to quickly decline after acute abstinence. The acupuncture treatment will greatly reduce these to a tolerable or insignificant level and the subject can maintain with little or no urges to smoke. By the second day there is sufficient plasma nicotine to cause the initial experience of
withdrawal. Therefore it is extremely important that the treatments be provided on contiguous days for nicotine and all other substances as well. If a one day break is allowed between the two treatments, a large percentage of smokers cannot make it through the second day without smoking because of the development of withdrawal symptoms. Also, a small percentage of people, perhaps 1 to 2%, may require a third treatment, usually provided on the third day, probably because their bodies are not breaking down the nicotine as fast. On rare occasion an individual might have withdrawal from nicotine that seems as severe as opiate withdrawal and they need to be treated with the protocol for opiates in order to be successfully detoxified from nicotine addiction. This may indicate some disorder in their liver function.

**Treatment and Schedule for Nicotine and Marijuana**

**Auricular Points:** Shenmen, Lung 2.

**Body Points:** Hegu (LI4), Taichong (Liv3)

**Electroacupuncture:** From Shenmen (Positive) to Lung 2 (Negative) ipsilaterally on each ear.

**Frequency:** 2 Hz. (Continuous Mode).

**Duration:** 30 to 35 Minutes.

**Schedule:** One treatment each day for two consecutive days.

**Follow Up:** Subject should be advised to seek acupuncture treatment anytime that strong urges or uncontrollable craving to smoke occur prior to actually smoking.

**Cocaine Treatment Protocol**

Both cocaine and alcohol withdrawal is treated once per day over a five day period. The only difference in the two treatments is that Kidney Channel points are used in respect to alcohol. The metabolic detoxification profile for both cocaine and alcohol is assumed to be approximately seven to ten days (See Figure 3). This is borne out by the clinical observation that after the fourth treatment there are virtually no withdrawal symptoms in either cocaine or alcohol subjects that are being treated. Many have felt that the fifth treatment was not even required although many others did need the final treatment. As in all the other treatment approaches no additional cocaine is used after the...
first treatment. Usually the subject is scheduled to begin treatment on a Monday morning so they are
advised to rid their homes, work place, automobiles, etc. of cocaine and advise their suppliers that
for health, legal and what ever reasons they are giving up the use. Ideally, they should not use any
cocaine over the week end before treatment if that is possible. Because of potential for withdrawal or
intense craving brought on by abrupt abstinence many cannot make it through the week end without
the drug.

During the initial interview or consultation it is important to ask if there are other users in the
immediate relationship indicating a possible co-addict situation which is often present in the use of
alcohol. Although this is not presently common in cocaine use or opiates it is important to ask since it
is very difficult to successfully treat one person in a relationship if they are constantly exposed to the
physical and emotional pressures to continue the use of the drug. Smith (1988) observed that
frequently the main problem of “crack mothers” was living with a male companion who was a heavy

\[ \text{Detox and Withdrawal Profile} \]

\[ \text{Figure 3. Detoxification and Withdrawal Profile for Either Cocaine or Alcohol} \]

\[ \text{With Overlay Representing Treatment (Tx) Over Five Consecutive Days} \]

\textbf{Treatment and Schedule for Cocaine}

\textbf{Auricular Points}: Shenmen. Lung 2.

\textbf{Body Points}: Hegu (LI4), Taichong (LV3)

\textbf{Electroacupuncture}: From Shenmen (Positive) to Lung 2 (Negative) ipsilaterally on each ear.

\textbf{Frequency}: 2 Hz. (Continuous Mode).

\textbf{Duration}: 30 to 35 Minutes.

\textbf{Schedule}: One treatment each day for five consecutive days.

\textbf{Follow Up}: A single follow up treatment is advisable at 3 and 6 weeks after the first course of
treatments. Subject should be advised to seek acupuncture treatment anytime that strong urges or
uncontrollable cravings to use cocaine occur prior to actually taking the drug. Should the subject inadvertently use cocaine or be coerced into trying cocaine, they should be advised to immediately come in as soon as possible for a follow up treatment.

**Alcohol Treatment Protocol**

Alcohol is treated over a five day period with one treatment each day (See Figure 3.). The only difference in this approach compared to cocaine is the addition of two acupuncture points on the leg. The withdrawal characteristics are much different from either cocaine or nicotine because the metabolic detoxification brings on changes in the acid base balance. This is manifested by the development of respiratory alkylosis within 12 to 36 hours after abstaining from alcohol in some chronic users. Acupuncture virtually eliminates the physiological effects of this condition which causes the subject to avoid full development of delirium tremors and hallucinations. Nervousness and irritability may be the only symptoms to be observed by some individuals. On rare occasions this nervousness may necessitate a second treatment on that particular day.

Frequently in the case of alcohol there is a co-alcoholic in the immediate relationship with the patient and it is advisable to treat them both at the same time. Often they can be scheduled to come into the clinic at the same time providing there are no underlying hostilities between the two parties. Often alcoholics have close drinking buddies that, for whatever reason, feel they will lose the friendship of a person that becomes sober. So they will continue to urge the person to have a few drinks to get them back into the group. This “group acceptance” type peer pressure is also seen with other drugs as well.

**Treatment and Schedule for Alcohol**

**Auricular Points:** Shenmen, Lung 2.
**Body Points:** Hegu (Li4), Taichong (Liv3), Zhubin (Kid9), Fuliu (Kid7)
**Electroacupuncture:** From Shenmen (Positive) to Lung 2 (Negative) ipsilaterally on each ear.
**Frequency:** 2 Hz. (Continuous Mode).
**Duration:** 30 to 35 Minutes.
**Schedule:** One treatment each day for five consecutive days.
**Follow Up:** A single follow up treatment is advisable at 3 and 6 weeks after the first course of treatments. Subject should be advised to seek acupuncture treatment anytime that strong urges or uncontrollable cravings to drink occur prior to actually using alcohol. Should the subject inadvertently drink or be coerced into trying a drink of alcohol, they should be advised to immediately come in as soon as possible for a follow up treatment.

**Opiate Treatment Protocol**

The potential withdrawal from opiates is quite significant and involves CNS receptors plus those in the gastrointestinal tract. In addition to a wide range of reactions, symptoms can also include cramps, constipation and backache. Pain in the low back will sometimes manifest during the actual treatment and the Chinese “Tuina” massage is applied to the back even though the patient is lying on their back. This is accomplished by reaching under the subject to manipulate the area of the low back. Sometimes the patient is given mild stimulation to the back with a plum blossom needle device after the regular treatment. It may take seven to ten days for the opiates to clear the body to the point where withdrawal is not experienced. Because the symptoms are quite profound, two treatments per day are needed for the first three days followed by daily treatments for three more days (See Figure 4.). The total of nine treatments is provided to match the potential detoxification and withdrawal profile.

The heroin and methadone subjects seem quite apprehensive about being needled, especially on the ears, since most are on the verge of abstinence syndrome when they arrive in the morning for the first treatment on the first day. In this situation the four points on the hand and feet (Hegu and
Taichong) are inserted first followed by Zhubin and Fuliu on the leg. After this the patient starts to relax and then the two ear points (Lung 2 and Shenmen) can be inserted. Electroacupuncture stimulation is first applied on Zhubin to Fuliu, ipsilaterally on each leg, for about 15 minutes duration prior to providing stimulation on the ear points. The ear points are stimulated for an additional 30 minutes, making the total duration of 45 minutes.

Treatment usually always starts on a Monday morning and the patient is almost always scheduled first or even sometimes early before regular clinic hours. The reason for this is that the subject has not had any drugs since the night before and when they arrive at the clinic they are starting to feel signs of withdrawal. The second treatment is nominally scheduled for mid to late afternoon, however, since there is no way to predetermine how long the patient can go before withdrawal discomfort starts. The patient is advised that even though they have a nominal appointment for the second treatment that day they should come in immediately should they feel they can not wait for the scheduled time slot. For an outpatient treatment protocol, one should be aware that the opiate addict will usually show up quite early for the treatments on subsequent days.

As noted above, two treatments, one in the early morning and one in late afternoon are provided for the first three days. One treatment each morning is then provided for the next three days.
Occasionally a third treatment is provided on the first day although almost all make it through with the scheduled two. Also, on occasion a patient may require two treatments on the fourth day, but this is usually rare. Some treatment approaches for in patient care involved staying with the addict and providing treatment whenever abstinence symptoms presented (Kao and Lu, 1974). Single follow up treatments are essential for opiate addicts, usually scheduled at one, three and six weeks after completing the first course of treatments. It seems that former addicts have poorer coping skills to handle subsequent stress exposure. Therefore they are encouraged to seek treatment when stress is high.

One interesting observation about opiate addicts is that often they do not want to pay for their treatments or they try to find a way of not paying, such as writing bad checks. Whether this observation is related to long time behavior patterns of surviving with opiate addiction is not known.

**Treatment and Schedule for Heroin, Methadone and other Opiates**

**Auricular Points:** Shenmen, Lung 2.

**Body Points:** Hegu (LI4), Taichong (Liv3), Zhubin (Kid9), Fuliu (Kid7)

**Electroacupuncture:** Zhubin (Kid9) (Positive) to Fuliu (Kid7) (Negative) ipsilaterally on each leg for 15 minutes duration and then change application to the ear from Shenmen (Positive) to Lung 2 (Negative) ipsilaterally on each ear for an additional 30 minutes.

**Frequency:** 2 Hz. (Continuous Mode).

**Duration:** 45 Minutes.

**Schedule:** Two treatments each day for first three days and then one treatment each day for an additional three days (nine treatments over six consecutive days)

**Follow Up:** A single follow up treatment is advisable at the end of 1, 3, and 6 weeks after the first course of treatments. Subject should be advised to seek acupuncture treatment anytime that strong urges or uncontrollable craving to use drugs occur prior to actually taking the drugs. Should the subject inadvertently use drugs or be coerced into trying drugs, they should be advised to immediately come in as soon as possible for one (1) or more follow up treatments.
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53. Pomeran}
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The Effect of Stimulus Frequency on the Analgesic Response to Percutaneous Electrical Nerve Stimulation in Patients with Chronic Low Back Pain

El-sayed A. Ghoname, MD, William F. Craig, MD, Paul F. White, PhD, MD, FANZCA, Hesham E. Ahmed, MD, Mohamed A. Hamza, MD, Noor M. Gajraj, MD, Akshay S. Vakharia, MD, and Carl E. Noe, MD

Eugene McDermott Center for Pain Management, Department of Anesthesiology & Pain Management, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

Low back pain (LBP) is one of the most common medical problems in our society. Increasingly, patients are turning to nonpharmacologic analgesic therapies such as percutaneous electrical nerve stimulation (PENS). We designed this sham-controlled study to compare the effect of three different frequencies of electrical stimulation on the analgesic response to PENS therapy. Sixty-eight consenting patients with LBP secondary to degenerative lumbar disc disease were treated with PENS therapy at 4 Hz, alternating 15 Hz and 30 Hz (15/30 Hz), and 100 Hz, as well as sham-PENS (0 Hz), according to a randomized, cross-over study design. Each treatment was administered for a period of 30 min three times per week for 2 wk. The pre- and posttreatment assessments included the health status survey short form and visual analog scales for pain, physical activity, and quality of sleep. After receiving all four treatments, patients completed a global assessment questionnaire. The sham-PENS treatments failed to produce changes in the degree of pain, physical activity, sleep quality, or daily intake of oral analgesic medications. In contrast, 4-Hz, 15/30-Hz, and 100-Hz stimulation all produced significant decreases in the severity of pain, increases in physical activity, improvements in the quality of sleep, and decreases in oral analgesic requirements \((P < 0.01)\). Of the three frequencies, 15/30 Hz was the most effective in decreasing pain, increasing physical activity, and improving the quality of sleep \((P < 0.05)\). In the global assessment, 40% of the patients reported that 15/30 Hz was the most desirable therapy, and it was also more effective in improving the patient’s sense of well-being. We conclude that the frequency of electrical stimulation is an important determinant of the analgesic response to PENS therapy. Alternating stimulation at 15-Hz and 30-Hz frequencies was more effective than either 4 Hz or 100 Hz in improving outcome measures in patients with LBP. Implications: The frequency of electrical stimulation seems to be an important determinant of the analgesic efficacy of percutaneous electrical nerve stimulation. Mixed low- and high-frequency stimulation was more effective than either low or high frequencies alone in the treatment of patients with low back pain.

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Concerns regarding the efficacy and side effects associated with these treatment modalities have increased interest in nonpharmacologic neuromodulation therapies such as transcutaneous electrical nerve stimulation (TENS) (6), acupuncture (7,8), electroacupuncture (9), and percutaneous electrical nerve stimulation (PENS) (10–12). Unfortunately, most of the published studies involving the use of electrical stimulation devices have used arbitrarily chosen treatment variables. Therefore, we designed a randomized, sham-controlled, cross-over study to evaluate the effect of stimulation frequency on the acute analgesic response to PENS therapy. The comparative effects of three different frequencies of stimulation (4 Hz, alternating...
15 Hz and 30 Hz, and 100 Hz) on pain scores, physical activity, quality of sleep, and the patient's sense of well-being were evaluated in patients with LBP.

**Methods**

After obtaining institutional review board approval and written informed consent, 68 patients (30 men and 38 women) with LBP associated with radiologically confirmed degenerative lumbar disc disease were enrolled in this randomized, sham-controlled, investigator-masked, cross-over study. Each patient was treated with sham-PENS (no electrical stimulation) and PENS at 4 Hz, alternating 15 Hz and 30 Hz (15/30 Hz) (a mixed frequency using both frequencies at each cycle with the stimulation pulses switched on and off every 3 s), and 100 Hz for a period of 30 min, three times per week for 2 consecutive wk in a random sequence (with 1 wk off between each treatment modality). Inclusion criteria included a history of LBP that has remained unchanged on a stable oral nonopioid analgesic regimen for a period of at least 3 mo before enrolling in the study. Exclusion criteria included LBP with a radicular component (sciatica), a history of drug or alcohol abuse, major organ disease, a change in the character or severity of the pain within the last 3 mo, and an inability to reliably complete the health status survey short form (SF-36), the daily assessment tools, or the global assessment questionnaire.

The basic therapy consists of the placement of ten 32-gauge (0.2 mm) stainless steel acupuncture-like needle probes (ITO, Tokyo, Japan) into the soft tissue and/or muscle in the low back region to a depth of 2–4 cm according to the dermatomal distribution of the pain as illustrated in Figure 1. The 10 probes were connected to five bipolar leads (with each lead connected to one positive and one negative probe) from an investigational (non-Food and Drug Administration-approved), low-output electrical generator, which was calibrated before each series of treatments. The maximal amplitude of the electrical stimulation produced by the generator was 25 mA, with a unipolar square-wave pattern and a pulse width of 0.5 ms. The electrical current was DC, and the duty cycle was continuous. These probes were then stimulated at one of four different frequencies: 0 Hz (sham), 4 Hz, 15/30 Hz, or 100 Hz. The intensity of the electrical stimulation was adjusted to produce the highest tolerable electrical sensation without muscle contractions (except for the sham treatments).

Before initiating the first of the four (frequency) treatment modalities, patients were required to complete the SF-36 (13). The physical component summary (PCS) and mental component summary (MCS) scores were used to assess the patient's response to each of the therapeutic modalities (14). The baseline level of pain, physical activity, and quality of sleep was evaluated before the first treatment with each modality using standard 10-cm visual analog scales (VAS), with 0 = best to 10 = worst. Repeat VAS assessments of pain, activity, and sleep were performed three times per week before each treatment session. In addition, the pain VAS was repeated 5–10 min after each treatment session. The daily oral analgesic requirements (pills per day) were recorded in the patient's diary during each phase of the study. The SF-36 questionnaire was repeated after completing all six treatment sessions with each of the four frequency modalities. Finally, each patient completed a global assessment questionnaire comparing the relative effectiveness of the sham and the three stimulation frequencies 72 h after the final treatment session.

The NCSS software package (version 6.0.1; NCSS, Kaysville, UT) was used for all statistical analyses. An *a priori* power analysis with $\alpha = 0.05$, $\beta = 0.10$ (power 90%) and $\delta = 2.0$ determined that a group size of 60 should be adequate to demonstrate a difference of 25% among the pain VAS scores for the four frequencies.
studied. The changes in the VAS scores were analyzed using repeated-measures analysis of variance and Student's t-test, with a Bonferroni correction applied for multiple comparisons. Analysis of discrete data was performed by using the χ² test. Changes and differences in the SF-36 scores were analyzed by using paired sample t-tests. Data are presented as mean values ± SD, median values, and percentages. P < 0.05 was considered statistically significant.

Results

The prestudy SF-36 evaluation suggested that this LBP patient population (age 46 ± 21 yr) reported significantly lower health-related quality of life scores compared with the general population. The median prestudy scores were 29.8 and 41.4 for the PCS and MCS, respectively, compared with general population norms of 50 for these two variables. The posttreatment SF-36 test results revealed that the 4-Hz, 15/30-Hz, and 100-Hz frequencies produced significant improvements over the prestudy scores for both the PCS and the MCS components (P < 0.01). Moreover, the absolute (mean) magnitude of the changes in PCS and MCS components at the end of each treatment period were similar with 4 Hz (7.0 and 2.8, respectively), 15/30 Hz (7.3 and 3.2, respectively), and 100 Hz (7.1 and 3.1, respectively). In contrast, the sham treatments did not show any significant improvement in posttreatment functionality.

All three frequencies of electrical stimulation produced significant decreases in the pain scores immediately after each treatment (Table 1). Compared with the sham treatments, the 4-Hz, 15/30-Hz, and 100-Hz frequencies of PENS therapy also produced statistically greater decreases in the degree of pain and improved physical activity and sleep quality at the end of the 2-wk treatment period (Fig. 2). However, the overall percent changes in pain, physical activity, and quality of sleep scores were significantly greater after electrical stimulation at 15/30 Hz compared with 4 Hz or 100 Hz.

The daily requirements for nonopioid analgesic medications are summarized in Figure 3. Compared with baseline values 24 h before starting each frequency modality, the need for oral analgesic medications was significantly decreased over the course of the 2-wk treatment period with 4 Hz, 15/30 Hz, and 100 Hz, but not with the sham treatments. Moreover, the overall percent decrease in the oral analgesic requirements was greater with 15/30 Hz (48%) than with 4 Hz (35%) or 100 Hz (33%).

Finally, the global assessment of the four modalities indicated that 15/30 Hz was the therapy preferred by 40% of the patients, whereas 28%, 30%, and 2% favored the 4 Hz, 100 Hz, and sham treatments, respectively (Table 2). In addition, the 15/30-Hz treatments were significantly more effective in improving the patient's physical activity and sense of well-being compared with the 4-Hz, 100-Hz, and sham treatments. Given a hypothetical situation, patients indicated that they would be more willing to pay out-of-pocket for the PENS treatment when it was administered at a frequency of 15/30 Hz (versus the sham treatment).

Discussion

Analogous to previously reported findings in animals with electroacupuncture (15), these data suggest that the frequency of electrical stimulation influences the analgesic response to PENS therapy in patients with chronic LBP. Compared with low- (4 Hz) and high- (100 Hz) frequency stimulation, a mixed pattern (15/30 Hz) of electrical stimulation produced the greatest decrease in pain and improvement in physical activity and quality of sleep at the end of a 2-wk treatment period.

Using a rat model for studying electroacupuncture, Chen et al. (15) reported that the dense-disperse mode of electrical stimulation (alternating 2 Hz and 15 Hz) was more effective than a fixed frequency of stimulation at either 2 Hz or 100 Hz in producing experimental analgesia. According to Sun and Han (16), the enhanced analgesia produced by alternating frequencies results from the differing effects of the frequency of stimulation on the pattern of neurotransmitter release within the central nervous system (CNS). At

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Table 1. Comparison of the Effects of the Four Frequency (F) Modalities on the VAS Pain Scores

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sham</th>
<th>F4</th>
<th>F15/30</th>
<th>F100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>5.8 ± 1.5</td>
<td>6.4 ± 1.6</td>
<td>6.0 ± 1.7</td>
<td>5.7 ± 1.6</td>
</tr>
<tr>
<td>Post</td>
<td>5.6 ± 1.8</td>
<td>2.3 ± 1.2*</td>
<td>2.5 ± 1.3*</td>
<td>2.7 ± 1.5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>5.9 ± 1.8</td>
<td>6.1 ± 1.7</td>
<td>5.4 ± 1.7</td>
<td>5.4 ± 1.8</td>
</tr>
<tr>
<td>Post</td>
<td>5.5 ± 1.6</td>
<td>2.1 ± 1.4*</td>
<td>2.3 ± 1.3*</td>
<td>2.5 ± 1.3*</td>
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<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>5.8 ± 1.7</td>
<td>5.9 ± 1.8</td>
<td>5.1 ± 2.0</td>
<td>5.1 ± 1.9</td>
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<tr>
<td>Post</td>
<td>5.7 ± 1.8</td>
<td>2.5 ± 1.2*</td>
<td>2.5 ± 1.4*</td>
<td>2.2 ± 1.5*</td>
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<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>5.6 ± 1.6</td>
<td>5.1 ± 1.5</td>
<td>4.9 ± 1.6</td>
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</tr>
<tr>
<td>Post</td>
<td>5.5 ± 1.9</td>
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<td>1.7 ± 1.3*</td>
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<tr>
<td>Pre</td>
<td>5.9 ± 1.7</td>
<td>4.9 ± 1.8</td>
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<td>6</td>
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<td></td>
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<tr>
<td>Pre</td>
<td>5.7 ± 1.7</td>
<td>4.7 ± 1.6</td>
<td>4.0 ± 1.4</td>
<td>4.5 ± 1.5</td>
</tr>
<tr>
<td>Post</td>
<td>5.5 ± 1.8</td>
<td>1.2 ± 1.2*</td>
<td>1.1 ± 1.4*</td>
<td>1.2 ± 1.5*</td>
</tr>
</tbody>
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Values are mean ± SD. VAS = visual analog scale, with 0 = no pain to 10 = worst pain imaginable. *Significantly different from values before (pre) each treatment session (P < 0.01).
2 Hz, analgesia was alleged to be mediated by stimulation of μ and δ opioid receptors, whereas, at 100 Hz, analgesia was reportedly mediated by activation of κ opioid receptors in the CNS (16).

In studying the effect of the frequency of electroacupuncture stimulation on the release of substance P in the spinal cord, Chen et al. (17) also found that 15 Hz was more effective than either lower (2, 4, or 8 Hz) or higher (30 or 100 Hz) frequencies of electrical stimulation. Analogous to the findings of Sun and Han (16), Goldstein and Naidu (18) also reported that high-frequency (100 Hz) electroacupuncture-induced analgesia was mediated by the activation of κ opioid receptors, whereas low-frequency stimulation (2 Hz) activated μ and δ opioid receptors. One might speculate that using a combination of intermediate frequencies (e.g., alternating 15 Hz and 30 Hz) would activate both subtypes of opioid receptors. However, opioid receptor binding studies would have to be performed to determine the pattern of opioid receptor activation that occur when mixed frequencies of electrical stimulation are used to produce electroanalgesia in humans.

Controversy still surrounds the optimal frequency of electrical stimulation for TENS therapy (19). For example, Walsh et al. (20) reported that a low frequency (4 Hz) of stimulation had a greater hypoalgesic effect than high-frequency (100 Hz) stimulation using an experimental pain model. However, Johnson et al. (21) reported that using high-frequency stimulation (20–80 Hz) produced greater analgesic effects than low-frequency stimulation (10 Hz). Consistent with our findings using PENS therapy, Hansson and Ekblom (22) reported significant pain relief at both high and low frequencies of electrical stimulation. In a recent TENS study, Hamza et al. (23) found that mixed-frequency electrical stimulation at 2 and 100 Hz produced greater postoperative analgesic-sparing effects than either 2 Hz or 100 Hz alone. Thus, it seems that both PENS and TENS therapies are most effective when administered using mixed frequencies of electrical stimulation.

The deficiencies in the current study design relate to an inability to effectively blind the patients, although a sham treatment was included because of the unique nature of the electrical sensation produced by the active PENS treatments. In an attempt to minimize investigator bias, all patient assessments were performed by one of the investigators not involved in actually administrating the PENS therapy. To avoid
Table 2. Overall Patient Evaluation of the Relative Effectiveness of the Three Different Frequencies (F) and Sham Therapies After All Six Treatment Sessions with Each Modality

<table>
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<tr>
<th></th>
<th>Sham</th>
<th>F 4</th>
<th>F 15/30</th>
<th>F 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most desirable modality</td>
<td>2</td>
<td>28*</td>
<td>40**+</td>
<td>30*</td>
</tr>
<tr>
<td>Improved physical activity</td>
<td>3</td>
<td>30*</td>
<td>38**+</td>
<td>29*</td>
</tr>
<tr>
<td>Improved sense of well-being</td>
<td>5</td>
<td>23*</td>
<td>44**+</td>
<td>28*</td>
</tr>
<tr>
<td>Preferred pain therapy</td>
<td>2</td>
<td>28*</td>
<td>40**+</td>
<td>30*</td>
</tr>
<tr>
<td>Willing to pay extra for therapy</td>
<td>3</td>
<td>25*</td>
<td>45**+</td>
<td>27*</td>
</tr>
</tbody>
</table>

Values are expressed as percentages.

* Significantly different from the sham treatments (P < 0.05).
† Significantly different from the F 4 treatments (P < 0.05).
‡ Significantly different from the F 100 treatments (P < 0.05).

Figure 3. Changes in the daily oral intake of nonopioid analgesic medications (pills per day) during the 2-wk treatment period with each of the four frequency modalities. Data are mean values ± SEM. * P < 0.05 and † P < 0.01 compared with values 24 h before the first treatment (baseline).

In conclusion, using a mixed frequency (alternating 15 Hz and 30 Hz) of PENS was more effective than either low (4 Hz) or high (100 Hz) frequencies alone in improving short-term outcome measures in patients with LBP.