

The Short- and Long-Term Benefit in Chronic Low Back Pain Through Adjuvant Electrical Versus Manual Auricular Acupuncture

Sabine M. Sator-Katzenschlager, MD*, Gisela Scharbert, MD*,
Sibylle A. Kozek-Langenecker, MD*, Jozef C. Szeles, MD†, Gabriele Finster, MD*,
Andreas W. Schiesser, PhD‡, Georg Heinze, PhD§, and Hans Georg Kress, MD, PhD*

From the *Department of Anesthesiology and Intensive Care Medicine (B), Outpatient Pain Center, the †Department of Vascular Surgery, the ‡Ludwig Boltzmann Institute of Consciousness Psychology and Transculture Psychotherapy, and the §Department of Medical Computer Science, University of Vienna, Vienna, Austria

Acupuncture is an established adjuvant analgesic modality for the treatment of chronic pain. Electrical stimulation of acupuncture points is considered to increase acupuncture analgesia. In this prospective, randomized, double-blind, controlled study we tested the hypothesis that auricular electroacupuncture (EA) relieves pain more effectively than conventional manual auricular acupuncture (CO) in chronic low back pain patients with insufficient pain relief (visual analogue scale [VAS] ≥ 5) treated with standardized analgesic therapy. Disposable acupuncture needles were inserted in the auricular acupuncture points 29, 40, and 55 of the dominant side and connected to a newly developed battery-powered miniaturized stimulator worn behind the ear. Patients were randomized into group EA ($n = 31$) with continuous low-frequency auricular EA (1 Hz biphasic constant current of 2 mA) and group CO ($n = 30$) without electrical stimulation (sham-electroacupuncture). Treatment was performed once weekly for 6 wk, and in each group needles were

withdrawn 48 h after insertion. During the study period and a 3-mo follow-up, patients were asked to complete the McGill questionnaire. Psychological well being, activity level, quality of sleep, and pain intensity were assessed by means of VAS; moreover, analgesic drug consumption was documented. Pain relief was significantly better in group EA during the study and the follow-up period as compared with group CO. Similarly, psychological well-being, activity, and sleep were significantly improved in group EA versus group CO, the consumption of analgesic rescue medication was less, and more patients returned to full-time employment. Neuropathic pain in particular improved in patients treated with EA. There were no adverse side effects. These results are the first to demonstrate that continuous EA stimulation of auricular acupuncture points improves the treatment of chronic low back pain in an outpatient population.

(Anesth Analg 2004;98:1359–64)

Low back pain affects a large proportion of the population in the developed world. Of the adult population, 60%–90% is at risk of developing low back pain at some point in their lives (1,2). Treatment goals are pain relief without adverse therapy-associated side effects and improvement of the patients' well being, activity, and sleep. Treatment options include conventional pharmacotherapy, invasive pain therapy, surgical interventions, and physiotherapy combined with psychological or complementary

approaches (3). Among the latter, acupuncture has become increasingly popular in western pain clinics (4). The theory of acupuncture is based on the concept that an imbalance of "Qi," an energy flow through hypothesized channels called "meridians" in the body, can be corrected by the manipulation of identifiable points close to the skin. In addition to the classical acupuncture points located on the "meridians," Nogier (5) described acupuncture points on the ear. Auricular acupuncture postulates a somatotopic relation of the ear with other anatomical regions (6,7).

Long-lasting pain relief after manual body acupuncture has been documented in chronic low back pain (8,9). Acupuncture has proven not only to be therapeutically beneficial but also to reduce medical health costs (10). Electrical stimulation of acupuncture points is

Accepted for publication October 30, 2003.

Address correspondence and reprint requests to Sabine Sator-Katzenschlager, MD, Department of Anesthesiology and Intensive Care Medicine (B), University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria. Address email to sabine.sator@univie.ac.at.

DOI: 10.1213/01.ANE.0000107941.16173.F7

considered to further increase acupuncture analgesia (11,12). However, no study exists on the potential benefits of continuous electrical auricular acupuncture (EA) in outpatients with chronic nonradicular low back pain. The present study was performed to test the hypothesis that electrical stimulation of auricular acupuncture points (EA) is more effective than conventional manual auricular acupuncture (CO) in those patients. A new, commercially available stimulator device was used that, for the first time, allows at home treatment of outpatients using continuously applied EA.

Methods

After obtaining approval from the institutional Ethics Committee at the University of Vienna and written informed consent, 87 otherwise healthy adult patients with chronic low back pain were investigated in a prospective, randomized, double-blind, controlled study. Inclusion criteria were lumbar or lumbosacral low back pain with a duration of at least 6 mo, normal neurologic function of lumbosacral nerves, and no pain radiation (nonradicular muscular and skeletal low back pain, such as spondylarthrosis or localized protusion of the disk). Exclusion criteria were allergy against lornoxicam or tramadol, history of drug abuse, pregnancy, concomitant use of transcutaneous nerve stimulation or pacemaker, and a history of acupuncture treatment.

Standardized Oral Analgesic Treatment

After an initial physical and neurological examination, patients received oral pharmacotherapy with 8 mg lornoxicam twice daily and a rescue medication with up to 8 times 50 mg tramadol daily. After 1 wk, the participants were reevaluated and asked to rate their pain intensity on a visual analog scale (VAS; 0 = no pain, 10 = worst pain imaginable). Patients were eligible for the next step in the present study if, despite medication, their persisting pain intensity was at least VAS 5.

Technical Features Of The Disposable EA Device

The stimulator consists of a microcontroller and a bit-coded ST62T60BM6 interface, which produce defined waves of electrical stimuli. The constant current source from three serial nickel metallic hydride (NiMH) cells with 1.2 V open circuit voltage guarantees equivalent stimulation energy regardless of the individual impedance of the skin. The P-Stim™ model used in the present study measures only 13 mm × 8 mm and is packed in a 20-pin Surfaced Mounted Device case. P-Stim™ has a Read Only Memory capacity of 4 kbyte static and 512 bytes dynamic space, using 5 interrupt

vectors with 8 MHz clock frequency. In the output stage, the current is amplified to drive 3 parallel stimulation channels. The frequency of stimulation was 1 Hz; the high phase was between 1 and 10 ms. After 3 h of stimulation a break of 3 h was programmed. For safety reasons the maximum current was limited to 4 mA for all channels, but in the default setting the trigger was only 1 mA per channel, adding up to 3mA. Reliability of the function mode was controlled by an integrated watchdog and automatically switched off by low accu voltage.

Study Protocol

Patients with insufficient pain relief (VAS \geq 5) using continuous oral pharmacotherapy were randomized into 2 groups using computer-generated random tables. All patients received CO using special titan disposable needles (27-gauge, 3 mm length; Biegler GmbH, Mauerbach, Austria) that were inserted on the dominant side at the following acupuncture points: lumbar spine, 40; shen men, 55; and cushion, 29 (Fig. 1). Acupuncture points were identified by measuring skin resistance using an electrical conductance meter (multipoint selection pen™, Biegler GmbH, Mauerbach, Austria). All needles were connected to the P-Stim™ device (Biegler GmbH, Mauerbach, Austria) positioned behind the ear like a hearing aid (Fig. 1). Those in group EA ($n = 31$) received continuous low-frequency EA using P-Stim™ (constant current: 1 Hz biphasic, 2 mA) over 48 h. For patients in group CO ($n = 30$) P-Stim™ devices were applied but without electrical stimulation (sham-EA). The P-Stim™ device was programmed by an independent technician. Patients and the doctor investigator were blinded as to the randomization.

The acupuncture needles with the P-Stim™ devices were withdrawn 48 h after insertion in all cases and the acupuncture treatment was performed once a week for 48 h at home, for a total study period of 6 wk. The follow-up assessment lasted 3 mo after the acupuncture series.

Outcome Variables

Of the eligible patients, 67 received questionnaires assessing pain intensity and quality, psychological well-being, activity level, and quality of sleep using VAS (0 = no impairment, 10 = worst impairment imaginable). Burning, lancinating, electrifying, and paroxysmal pain qualities were defined as neuropathic pain, whereas nociceptive (somatic or visceral) pain was classified as dull, aching, and cramplike or viselike pain. Furthermore, patients were asked to complete the McGill pain questionnaire, which allows patients to specify their subjective pain experience and includes an intensity scale and other items to determine the properties of pain experience (13). Analgesic

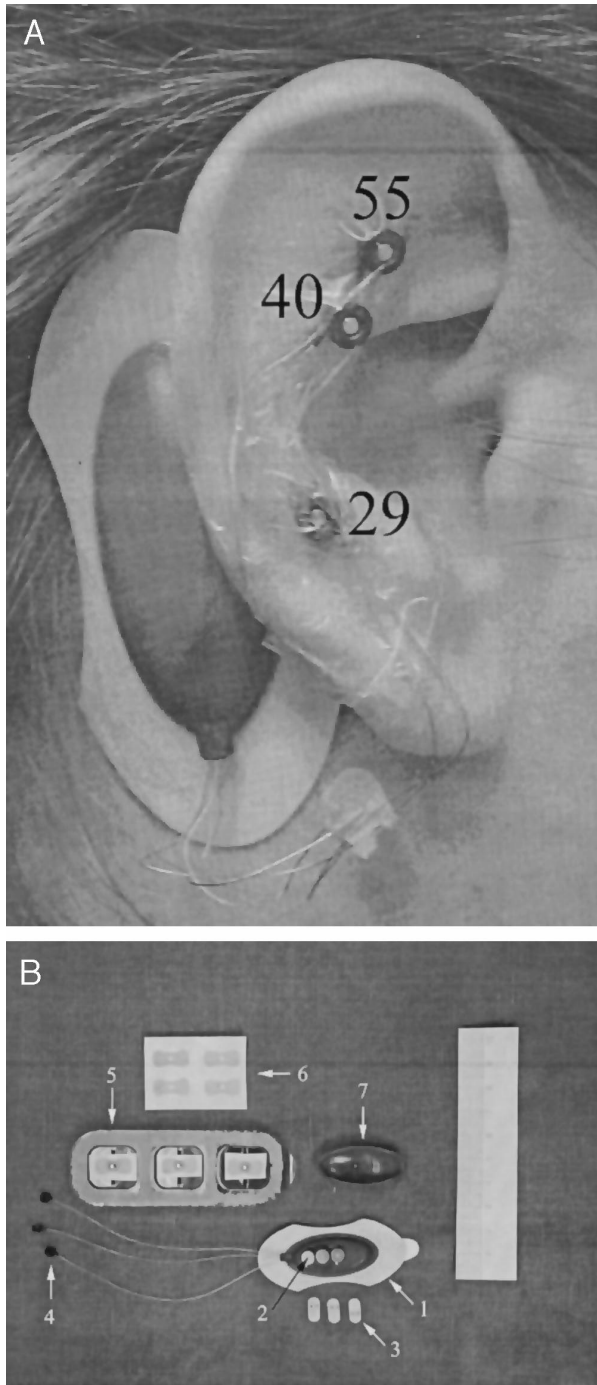


Figure 1. Electrical auricular point stimulation device (P-Stim™). A, acupuncture points are indicated by closed circles and numbered according to the nomenclature of Nogier (5): lumbar spine, 40; shen men, 55; and cushion, 29. B, disposable titan needles (#5) were inserted in the specific acupuncture points of the ear and fixed with adhesive tape (#6). Three wires (#4) are plugged into the acupuncture needles (#5), connected with the nickel metallic heart cells (#2), and the microcontroller and interface (#7). The constant current source of the P-Stim™ device guarantees equivalent stimulation energy (2 mA, 1 Hz biphasic) regardless of the individual impedance of the patient's skin. The P-Stim™ device is mounted on adhesive foam (#1) that keeps it behind the patient's ear. The batteries are protected by a cover (#3) to prevent accidental activation and energy loss before the intended start of operation (scale shown, 10 cm).

drug use was assessed, during the entire study period of 3 mo, 3 times daily (morning, afternoon, and evening). Demographic data, socioeconomic data, and side effects were documented. The patients' overall satisfaction with the acupuncture treatment was documented at the end of the study period.

In accordance with the intention-to-treat principle, data from all randomized patients were used for statistical analysis. Continuous and categorical variables were described by mean \pm SD and frequencies (percentages), respectively. Baseline values were compared using unpaired Student's *t*-tests. For each patient, daily mean values of VAS scores were calculated from three assessments per day (morning, afternoon, evening). From the daily mean values we calculated weekly mean values and overall mean values (average over 6 wk) per patient. Overall mean values and assessments after follow-up were compared using analysis of covariance. Weekly mean values were compared using repeated measurement analysis of covariance. For all analyses, group and sex were taken as factors and the respective baseline values (mean taken over 7 days before randomization) as covariate. *Post hoc* group comparisons performed at each week were corrected by the Bonferroni-Holm (14) method. Frequencies of categorical variables (pain qualities, socioeconomic status) after treatment were compared between groups using the Cochran-Mantel-Haenszel (15) test, stratifying for baseline categories. *P* values <0.05 were considered as statistically significant. The SAS System Version 8.2 (2001 SAS Institute Inc., Cary, NC) was used for statistical analysis.

Results

Eighty-seven patients were included. After the initial standardized drug treatment, 61 patients with VAS ≥ 5 were enrolled in the study (dropout because of VAS < 5 , $n = 26$). There were no significant differences in age, sex, pain history, and demographic data between the dropouts and the study group. During the study period, 6 patients (5 female/1 male) discontinued the treatment: 4 patients of group CO because of failed pain reduction, and 2 patients of group EA through noncompliance. Accordingly, 61 patients (43 women and 18 men) were analyzed.

There were no relevant differences in age (54.1 ± 12.3 yr versus 53.1 ± 12.1 yr), weight (77.4 ± 14.0 kg versus 74.2 ± 11.7 kg), or height (169.7 ± 7.9 cm versus 170.8 ± 8.3 cm) between group CO and group EA, respectively. Neither were there significant differences in the socioeconomic status of patients at the time of enrollment when comparing group CO and group EA: 9 versus 7 patients were retired, 12 versus 13 were on sick leave, 8 versus 10 were working full time, and 1 versus 1 were unemployed.

The mean duration of pain was 4.6 ± 1.0 yr, and there were no differences between the two groups. Of the 61 included patients, 36 had common low back pain of presumably muscular origin, whereas 25 had additional severe skeletal changes observed on radiograph and magnetic resonance imaging of the spine, including spondylarthrosis or localized protrusion of the disk. There were no differences in the proportion of muscular and skeletal low back pain between the two groups. The majority of patients had experienced various treatment modalities before entering the present study, including analgesic drugs, trigger point infiltrations, transcutaneous nerve stimulation, and passive physiotherapy including massage, warmth, and galvanization.

Despite randomization, there was a significant difference in pain scores at baseline in the first week before acupuncture between group CO and group EA, respectively (CO, 8.0 ± 0.8 ; EA, 7.5 ± 0.8 ; $P = 0.021$; Fig. 2A).

Pain intensity decreased in both groups during the study period. The reduction in pain intensity, however, was significantly more pronounced in group EA compared with group CO ($P < 0.001$; Fig. 2A). Pain relief lasted for the entire follow-up period of 3 mo. All patients in group EA responded positively to EA; there were no nonresponders. No gender differences were found. Pain was most intense in the morning in both groups throughout the study period (mean difference = VAS 0.16 when compared with afternoon scores; $P = 0.007$). Consumption of tramadol rescue medication was similar before the treatment but was significantly more during the entire investigation period in group CO when compared with group EA (150 versus 6 tablets; $P < 0.001$).

Frequencies of neuropathic pain decreased in 82% of patients from 11 (35%) to 2 (6%) in group EA and in only 54% from 15 (50%) to 7 (23%) in group CO ($P = 0.067$ difference between the groups). Frequencies of nociceptive pain decreased in 75% of patients from 20 (65%) to 5 (16%) in group EA and in 43% from 28 (93%) to 16 (53%) in group CO ($P = 0.009$).

Both groups showed improvement in these variables during the observation period. However, the increase in psychological well-being, physical activity, and quality of sleep during the 6-wk acupuncture treatment and follow-up was significantly more in group EA than in group CO (Fig. 2B-D). We did not find any significant sex-related differences in the response to acupuncture.

No adverse side effects of acupuncture (such as needle-induced hypotension, hematoma, or local auricular infection) were observed. Whereas, not surprisingly, all patients in group EA correctly identified electrical stimulation, 29 (97%) of the patients in group CO also believed they were receiving electrical stimulation. Twenty-seven (87%) of patients in group EA

were satisfied and would repeat the treatment if necessary; only 4 (13%) patients found the P-Stim™ design unpleasant and declined possible future treatment. All patients in group CO rejected further acupuncture treatment because of insufficient benefit. Fifteen percent of patients in group EA classified the P-Stim™ device as very good, 74% as suitable, and 11% as sufficient.

The socio-economic status of patients improved during the study period: 13 (41%) patients of group EA and 12 (40%) patients of group CO were on sick leave at the time of enrollment. After 3 mo, 10 (77%) patients of those on sick leave in group EA and 3 (25%) of these patients in group CO had returned to a full-time job ($P = 0.0032$ between the groups).

Discussion

In this study we demonstrated significant additional and long-lasting pain relief through adjunctive EA in patients suffering from chronic low back pain despite continuing oral analgesic therapy with a nonsteroidal antiinflammatory drug and the weak opioid tramadol (Fig. 2A). EA effectively reduced both neuropathic and nociceptive pain qualities. Not only did the patients' subjective pain assessment improve but objective variables such as the consumption of rescue medication also improved. Furthermore, patients treated with EA showed a significant improvement in psychological well being, physical activity, and quality of sleep (Fig. 2B-D). Patients receiving EA returned to full-time work earlier than patients treated with conventional manual acupuncture as a direct result of the increased quality of life.

The beneficial effect of acupuncture is still controversial (16-20). A meta-analysis of clinical trials of acupuncture for back pain showed that acupuncture is superior to various control interventions, although there is insufficient evidence to state whether it is superior to placebo (20). Our present data confirm and extend previous studies that showed a long-term pain-relieving effect of acupuncture in chronic pain patients (8,9,12). The mechanism of acupuncture analgesia remains in question, but biological responses such as the stimulation of A- δ fibers by the stimulating "De qi" sensation, as well as psychological aspects seem to be involved (17). Other potential mechanisms include the activation of descending inhibitory pain control systems (21,22), the activation of the propriospinal heterosegmental antinociceptive system leading to wind-down of pain-induced changes in signal transduction in the spinal cord (23), and the release of endogenous opioid peptides (24). EA has been found to induce the release of various neurotransmitters such as enkephalins and dynorphins (25) and substance P (26) in the central nervous system, both in animal studies and in

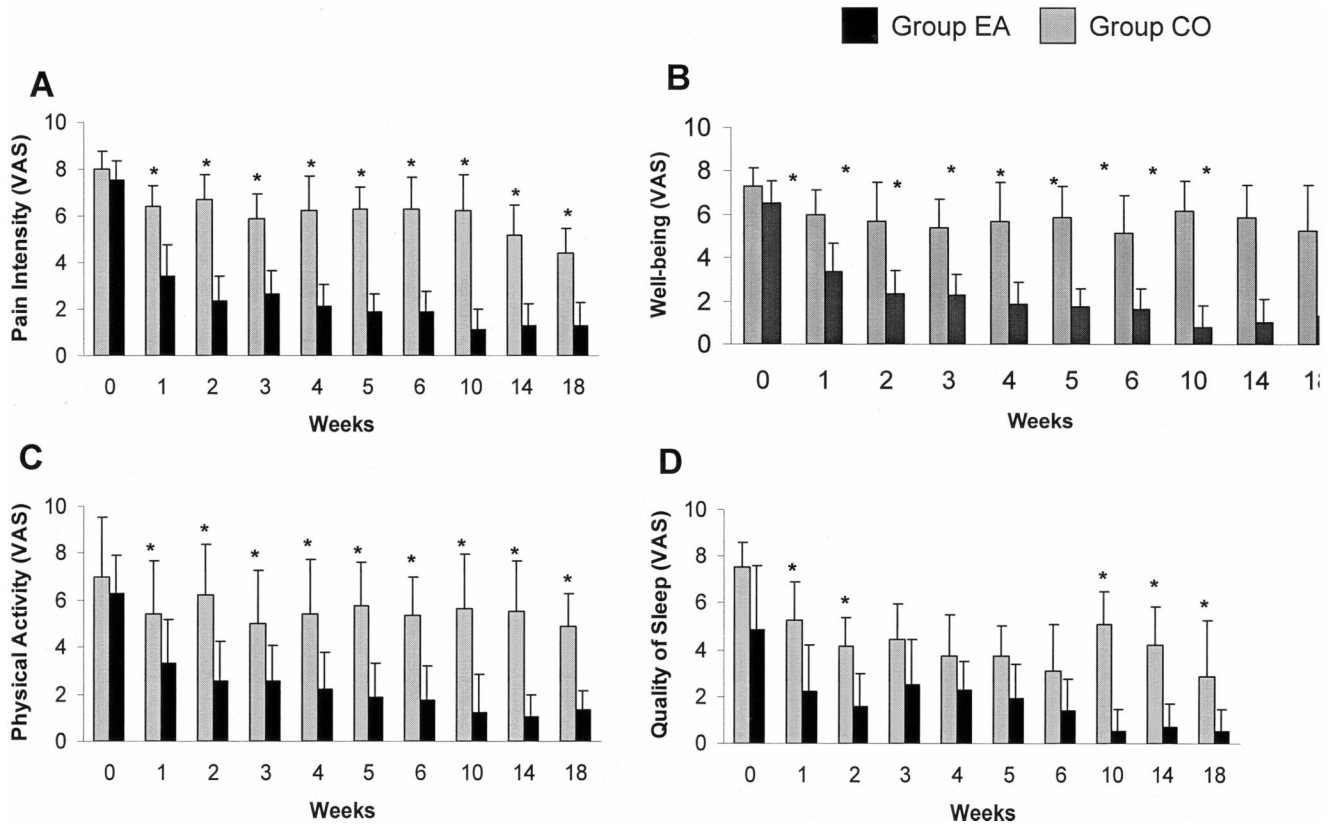


Figure 2. Effect of auricular electroacupuncture (group EA) versus sham-electroacupuncture (group CO) on pain intensity (2A), physical activity (2B), psychological well-being (2C), and the quality of sleep (2D) in chronic low back pain patients. From the first week on, the reduction in pain scores was significantly larger in group EA than in group CO (panel A). Similarly, psychological well-being (panel B), physical activity (panel C), and to some degree quality of sleep (panel D) significantly improved in patients of group EA during the 6-wk study period and the 3-mo follow-up. Data are presented as means \pm SD of subjective visual analog scales (VAS) ranging from 0 (no impairment) to 10 (worst deterioration imaginable). * $P < 0.05$ between the two groups.

humans (27). The specific electrical stimulation pattern may influence these analgesic effects (28). Both low- and high-frequency stimulation have been found to induce analgesia, but different types of endorphins are released depending on the stimulation pattern (24,29). Cumulative analgesic effects may be achieved by longer electrical stimulation periods (28).

In the present long-term follow-up study, we used EA where the analgesic effect is suggested to be mediated by a somatotopic relation of the ear points (acupuncture point 40) to the lumbar and sacral anatomical region (5-7). We used a self-adhesive and easy-to-apply miniaturized EA device that generates a biphasic low-frequency current to avoid polarization effects. Continuous electrical stimulation for 48 hours was applied at home, in contrast with other studies in which patients merely received body EA over half an hour in an outpatient clinic setting (8). This new, disposable device is commercially available in the United States, Europe, and South America.

Obviously, difficulties with blinding have always been discussed as a critical point of these studies and have proven to be one of the major problems for

adequate validation of the effectiveness of acupuncture (18,20). Electrical stimulation of the auricular acupuncture points permitted a fully double-blind study protocol in the current study. The stimulator was either activated or not by an investigator who was not otherwise involved in the study, electrical stimulation does not produce acoustical, tactile, or visual effects, and the stimulation unit is inside the device (Fig. 1). The results show that patients of both groups (100% EA versus 97% CO) believed they were receiving electrical stimulation, which proves that blinding was effective in patients who had no prior experience with acupuncture.

One limitation of the present study design, however, is the lack of a placebo-control group. The data presented cannot refute the hypothesis that all benefits from both treatments are attributable to nonspecific effects of participation in the study, contact with the pain therapist, or patient expectation.

Both CO and EA are inexpensive treatments with clear potential savings in overall costs, considering that chronic low back pain is a common cause of suffering, disability, and consumption of medical

health costs and social service use (30). Acquisition costs of one P-Stim™ set at the time of the treatment amount to 50 Euro. Unfortunately, the device cannot be reused by changing the batteries. The need for analgesic drugs was considerably less in patients of group EA, and patients were satisfied with pain treatment. This may prevent the temptation of seeking alternative pain control therapies and the phenomenon of "doctor shopping." It is important to carefully consider the consequences or outcome of the treatment (e.g., quality of life, resumption of normal activities, and social rehabilitation) in monetary terms (30). Together, our results indicate that substantial savings on medical health care can be made through the adjuvant use of EA.

The decreased consumption of analgesic drugs in patients of group EA decreases the risk of common drug-induced adverse side effects of nonsteroidal antiinflammatory drugs and opioids such as gastrointestinal bleeding, nausea, vomiting, obstipation, and dizziness (31,32).

Most important, we observed no adverse side effects of EA *per se* in any patient. We conclude that the use of EA acupuncture is safe (29). However, clinicians should be aware of contraindications against the use of an electrical stimulator device including the concomitant use of transcutaneous electrical nerve stimulation and/or pacemaker, as well as anticoagulation.

In summary, our results demonstrate that the treatment of chronic low back pain is significantly improved with regard to long-term clinical outcome through the use of electrical stimulation of auricular acupuncture points with the new P-Stim™ device.

References

1. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet* 1999;354:581-5.
2. Skovron ML, Szpalski M, Nordin M, et al. Sociocultural factors and back pain: a population-based study in Belgian adults. *Spine* 1994;19:129-37.
3. Wall PD, Melzack R. *Textbook of pain*. New York: Churchill Livingstone, 1994.
4. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;280:1569-75.
5. Nogier P. Face to face with auriculotherapy. *Acupunct Electrother Res* 1983;8:99-100.
6. Oleson T, Kroening RA. A comparison of Chinese and Nogier acupuncture points. *Am J Acupuncture* 1983;11:205-23.
7. Oleson T. *Auriculotherapy manual: Chinese and Western system of ear acupuncture*. 2nd ed. Los Angeles: Health Care Alternatives, 1996.
8. Carlsson CP, Sjolund BH. Acupuncture for chronic low back pain: a randomized placebo-controlled study with long-term follow-up. *Clin J Pain* 2001;17:296-305.
9. Molsberger AF, Mau J, Pawelec DB, Winkler J. Does acupuncture improve the orthopedic management of chronic low back pain. *Pain* 2002;99:579-87.
10. Carey TS, Garrett J, Jackman A, et al. The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors, and orthopedic surgeons. The North Carolina Back Pain Project. *N Engl J Med* 1995; 913-7.
11. Greif R, Lacity S, Mokhtarani M, et al. Transcutaneous electrical stimulation of an auricular acupuncture point decreases anesthetic requirement. *Anesthesiology* 2002;96:306-12.
12. White PF, Li S, Chiu JW. Electroanalgesia: its role in acute and chronic pain management. *Anesth Analg* 2001;92:505-13.
13. Melzack R. The short-form McGill pain questionnaire. *Pain* 1987;30:191-7.
14. Holm S. A simple sequentially rejective Bonferroni test procedure. *Scandinavian J Statistics* 1979;6:65-70.
15. Landis RJ, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. *Int Stat Rev* 1978;46:237-54.
16. Leibing E, Leonhardt U, Koster G, et al. Acupuncture treatment of chronic low-back pain: a randomized, blinded, placebo-controlled trial with 9-month follow-up. *Pain* 2002;96:189-96.
17. Ezzo J, Berman B, Hadhazy VA, et al. Is acupuncture effective for the treatment of chronic pain? A systematic review. *Pain* 2000;86:217-25.
18. Smith LA, Oldman AD, McQuay HJ, Moore RA. Teasing apart quality and validity in systematic reviews: an example from acupuncture trials in chronic neck and back pain. *Pain* 2000;86:119-32.
19. van Tulder MW, Cherkin DC, Berman B, et al. The effectiveness of acupuncture in the management of acute and chronic low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine* 1999;24: 1113-23.
20. Ernst E, White AR, Wider B. Acupuncture for back pain: meta-analysis of randomised controlled trials and an update with data from the most recent studies. *Schmerz* 2002;16:129-39.
21. Willer JC, Roby A, Le Bars D. Psychophysical and heterophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain* 1984;107:1095-112.
22. Anderson SA, Ericson T, Holmgren E, Hachisu M. Electroacupuncture: effect on pain threshold measured with electrical stimulation of teeth. *Brain* 1973;63:393-6.
23. Sandkühler J. The organization and function of endogenous antinociceptive systems. *Prog Neurobiol* 1996;1:49-81.
24. Mayer DJ. Biological mechanisms of acupuncture. *Prog Brain Res* 2000;122:457-77.
25. Han JS, Chen XH, Sun SL, et al. Effect of low- and high-frequency TENS on Met-enkephalin-Arg-Phe and dynorphin A immunoreactivity in human lumbar CSF. *Pain* 1991;47:295-8.
26. Tang NM, Dong HW, Wang XM, et al. Cholecystokinin antisense RNA increases the analgesic effect induced by electroacupuncture or low dose morphine: conversion of low responder rats into high responders. *Pain* 1997;71:71-80.
27. Ghone EA, Craig WF, White PF, et al. The effect of stimulus frequency on the analgesic response to percutaneous electrical nerve stimulation in patients with chronic low back pain. *Anesth Analg* 1999;88:841-6.
28. Hamza MA, Ghoname EA, White PF, et al. Effect of the duration of electrical stimulation on the analgesic response in patients with low back pain. *Anesthesiology* 1999;91:1622-7.
29. White PF, Craig WF, Vakharia AS, et al. Percutaneous neuro-modulation therapy: does the location of electrical stimulation effect the acute analgesic response? *Anesth Analg* 2000;91: 949-54.
30. Ghoname EA, Craig WF, White PF, et al. Percutaneous electrical nerve stimulation for low back pain. *JAMA* 1999;281:818-23.
31. Pietzsch M, Theuer S, Haase G, et al. Results of systematic screening for serious gastrointestinal bleeding associated with NSAIDs in Rostock hospitals. *Int J Clin Pharmacol Ther* 2002; 40:111-5.
32. Chapman SL, Byas-Smith MG, Reed BA. Effects of intermediate- and long-term use of opioids on cognition in patients with chronic pain. *Clin J Pain* 2003;18:83-90.