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Meta-Analysis of Randomized Controlled Trials of Cranial Electrostimulation

Efficacy in Treating Selected Psychological and Physiological Conditions

SIDNEY KLAWANSKY, M.D., PH.D.,[1] ALBERT YEUNG, M.D., SC.D.,[2] CATHERINE BERKEY, PH.D.,[1] NIRAV SHAH, B.S.,[1] HAI PHAN, B.S.,[1] AND THOMAS C. CHALMERS, M.D.[1]

To clarify the diverse published results of cranial electrostimulation (CES) efficacy, we conducted an extensive literature review that identified 18 of the most carefully conducted randomized controlled trials of CES versus sham treatment. For the 14 trials that had sufficient data, we used the techniques of meta-analysis to pool the published results of treating each of four conditions: anxiety (eight trials), brain dysfunction (two trials), headache (two trials), and insomnia (two trials). Because studies utilized different outcome measures, we used an effect size method to normalize measures which we then pooled across studies within each condition. The meta-analysis of anxiety showed CES to be significantly more effective than sham treatment ($p < .05$). Pooling did not affect results that were individually positive (headache and pain under anesthesia) or negative (brain dysfunction and insomnia). Most studies failed to report all data necessary for meta-analysis. Moreover, in all but two trials, the therapist was not blinded and knew which patients were receiving CES or sham treatment. We strongly recommend that future trials of CES report complete data and incorporate therapist blinding to avoid possible bias.

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Cranial electrostimulation (CES) is a therapeutic technique that uses low-level electrical signals applied to the head to treat a variety of conditions. Typically, electrodes are placed bilaterally over the eyelids and mastoid process.

Interest in CES began in the early 1900s. Investigators theorized that weak impulses of direct current applied transcranially would induce a sleep-like response and lead to a calming effect on the central nervous system. Much of the early work was conducted in the former Soviet Union and Eastern Europe. Researchers claimed success in treating diverse disorders, including depression, anxiety, insomnia, and psychosis. Attention to cranial electrotherapy in the West was stimulated by the International Symposia for Electrotherapeutic Sleep and Electroanesthesia, which was held in Graz, Austria, in 1966 and 1969 (Wagender, 1969; Wagender et al., 1969). However, many observers were skeptical about the claims for reasons of poor study design, lack of controls, and the nature of the outcome measures used (Iwanovsky and Dodge, 1968; Von Richthofen and Mellor, 1979; Wagender et al., 1969).

The net effect is that there is a body of research, published intermittently since early in the century and varying widely in study design and quality, suggesting the possibility that CES may be effective in treating a variety of psychological and physiological conditions.

Currently eight commercial devices for clinical application of CES are on the market.[3] In 1976, amendments to federal law regarding the U.S. Food and Drug Administration (FDA) brought medical devices that had already been marketed under FDA jurisdiction (Code of Federal Regulations, Title 21, Chapter 1). Makers of devices brought to market since that time have claimed "substantial equivalence" to the previously marketed devices. For example, the Neurotone device, one of the eight devices currently marketed, was designated for use in treating only insomnia, depression, and anxiety, since these are the only claims legally permitted for the newer devices.

In 1989, the FDA amended its device regulations to require all medical devices that had not previously done so to go through a formal premarket approval process. This process entails the submission of data adequate to support whatever claims of efficacy are to be made for the device, and, if requested, data supporting the

[1] Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts. Send reprint requests to Dr. Klawansky at Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Room LL-7, 677 Huntington Avenue, Boston, Massachusetts 02115.
[2] Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

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[3] R. Smith, LifeBalance International, personal communication, 1992.

safety of the device. The FDA has recently formally requested CES device manufacturers to comply with the requirement (Food and Drug Administration, 1993).

Experimenters have reported mixed results in treating a number of conditions, including anxiety, depression, pain, and insomnia (Feighner et al., 1973; Frankel et al., 1973; Passini et al., 1976; Rosenthal and Wulfsohn, 1970; Smith and Eleanor, 1977). An important quality of CES is its potential as a substitute for drug therapy for a number of conditions, such as anxiety, where drugs may have undesirable side effects or addictive potential.

Recent experimental work suggests that the collective behavior of cellular networks may recruit and aggregate the very low electrical voltages characteristic of individual cells (Grundler et al., 1992). The electrical aggregation may yield voltage levels comparable to and therefore responsive to the low voltage levels used in typical cranial electrostimulation devices. The resulting altered collective electrical properties in the brain's cellular network may, in turn, influence neurotransmitter activity.

In light of the theoretically desirable features of CES and the studies that have found benefit in its use, the current study aims primarily to clarify the validity of the diverse study results by using a meta-analytic approach. We propose to assess whether further exploration of this therapeutic modality might be warranted.

Methods

Literature Search

We assembled published trials of the efficacy of cranial electrostimulation in the treatment of a number of psychological and physiological conditions, including depression, anxiety, drug addiction insomnia, headache, and other pain. The optimal studies for our purpose are randomized control trials that compared CES with sham treatment in a double-blind manner.

We conducted several parallel literature searches for reported studies appropriate for inclusion in our analysis. We searched the MEDLINE database for the years 1966 to 1991, using a number of key words, including the terms electronarcosis and electric stimulation therapy. We attempted to identify publications not included in the MEDLINE database by soliciting bibliographies from investigators of CES and other sources. We reviewed the bibliographies of studies which we accepted as candidates for analysis as well as those of review articles and other sources (Smith, 1985; Taylor, 1990).

Although much of the early work was carried out in the former Soviet Union, a random sampling of recent studies published in Russia turned up only uncontrolled studies. Therefore, we excluded studies from this region and Eastern Europe and restricted our search to studies on human subjects published in English. We identified 18 randomized controlled trials (RCTs) of CES compared with sham treatment.

In Table 1, we summarize the features of the 18 studies. The study samples are generally small, with 12 studies having fewer than 50 patients.

Studies utilized a variety of CES devices. In this preliminary work, we did not attempt any analysis by signal parameters or treatment regimen.

Blinding of Participants

In 17 of the 18 RCTs (the exception was Stanley et al., 1982b), researchers attempted to provide a convincing sham treatment by attaching electrodes to the control patients to blind them to the treatment conditions. However, not all trials attempted to mimic in the control group the sensation induced by an actual current. In each treated group, the operator turned the current up until the patient felt a tingling sensation and then reduced the current to just below the reported threshold for the sensation. In the sham treatment arms that attempted to mimic the sensation experienced by the treated arm, the operator began the same way, but reduced the current to zero. In Table 1, we distinguished those trials that provided the sensation to the sham-treated patients from trials that did not. In either case, this procedure raises questions about adequate blinding of the therapist.

We read the Methods section of each study blinded to the results of the study in order to stratify the studies by level of blinding of the patient, therapist, and researcher/assessor and overall quality. For example, in Table 1 (Anxiety), Moore et al. (1975) and Krupitsky et al. (1991) characterized their studies as double-blind because the patient and assessor/researcher were blinded. However, in these studies the therapist was not blinded.

In studies for the treatment of anxiety, only in the Schmitt et al. (1986) and Hearst et al. (1974) studies did the researchers blind the therapist by presetting a circuit that either did or did not turn off stimulation after the initial setting. Similarly, in studies of the treatment of brain dysfunction (Table 1, Brain Dysfunction), only the Schmitt et al. (1984) study utilized a preset circuit to blind the therapist. The levels of blinding for anxiety, headache, brain dysfunction, insomnia, and operative pain are displayed in Table 1.

Quality of the Clinical Trial Reports

Because the results of any clinical trial may be distorted by unintended and structural biases, we followed a procedure of estimating a quality score (Chalmers et al., 1981), which might be useful in carrying out sensitivity analyses. To minimize the opportunities for bias to distort the scores, we had the papers blinded

TABLE 1
Description of RCTs of Cranial Electrostimulation

Author	No. of Patients (randomized)[a] CES	Sham	Total (*N* analyzed)	Diagnosis/Patient Type	Blinding[b] Patient	Therapist	Assessor	Authors' Description of Study Design	Outcome Measure[c]
				Anxiety					
1 Rosenthal (1971)	11	11	22 (22)	Neurotic, anxiety, depression, insomnia, agoraphobia, eczema	Yes−	Yes	No	Randomized double-blind	Clinical rating,* Zung self-rating depression scale
2 Tomsovic (1973)	18	16	29 (24)	Male alcoholic patients	Yes+	No	Interviewer	Randomized double-blind	N/A
3 Hearst (1974)	14	14	28 (28)	Psychiatrically ill patients	Yes+	Yes	Physician	Randomized double-blind	SRSS
4 Marshall (1974)	10	10	20 N/A	Depressive symptomatology	Yes+	No	Patient/ staff	Randomized	Self-rating, staff rating
5 Smith (1975)	18	18	38 (24)	Male alcholic patients	Yes+	No	No	Randomized	POMS*
6 Moore (1975)	8	9	17 (17)	Anxiety or depressive neurosis, personality disorders	Yes+	No	Patient	Randomized double-blind	TMAS*, clin asses by psych, BDI
7 Ryan (1976)	¢6 £6	¢6 £6	24 (24)	Psychiatric inpatients, VA hospital, nonpsychotic, nonneurological	Yes+	No	Patient	Randomized	STAI*, HSGHS
8 Passini (1976)	30	30	60 (60)	Alcohol/drug dependency (31), neurotic (11), psychotics (10), others (8)	Yes−	No	Patient	Randomized	MAACL, STAI*
9 Gomez (1978)	14	7 §7	28 (21)	Heroin addicts in VA methadone clinic	Yes−	No	Patient	Randomized	TMAS*, HAS
10 Schmitt (1986)	30	10 ¥20	40 (40)	Brain dysfunction in inpatient alcohol or polydrug users	Yes+	Yes	Patient	Randomized	STAI,* IPAT
11 Krupitsky (1991)	10	10	20 (20)	Alcoholic patients with affective disorders	Yes+	No	Patient	Randomized double-blind	TMAS,* Zung, Spielberger
				Brain Dysfunction					
1 Smith (1982)	50	50	100 (70)	Male volunteers, BD 2° to ETOH	Yes−	No	Yes	Randomized double-blind	Beta IQ,* 6 substudies*
2 Schmitt (1984)	30	10 ¥20	40 (32)	Brain dysfunction in inpatient alcohol or polydrug users	Yes+	Yes	Yes	Randomized double-blind	WAIS,* Rev. β,* IPAT, STAI, POMS
				Headache Pain					
1 Solomon (1985)	†18 •18	22	58 (58)	M/F with migraine and/or muscle contraction headaches	Yes+	No	Patient	Randomized	Headache Severity Score 1-10*
2 Solomon (1989)	50	50	100 (100)	M/F > 18 yr with tension headaches requiring analgesic agents > 1 yr	Yes+	No	Patient	Randomized double-blind	Headache Severity Score 1-10*
				Insomnia					
1 Weiss (1973)	5	5	10 (10)	Insomniacs	Yes+	Yes	Self	Randomized double-blind	Questionnaire 3 (0-3),* Sleep, Cornell Index, MMPI
2 Moore (1975)	8	9	17 (17)	Anxiety or depressive neurosis, personality disorders	Yes+	No	Patient	Randomized double-blind	Clinical insomnia (0-3),* clin asses by psych, depression, TMAS, BDI
				Operative Pain					
1 Stanley (1982b)	60	60*	120	Patients scheduled for urologic (90) or abdominal (30) surgery with N2 anesthesia ASA class II	No‡	Yes	Yes	Randomized single-blind	Painful memory,* somatic stimulation,* SBP heart rate, painful movement
2 Stanley (1982a)	25	25*	50	Patients scheduled for urologic surgery ASA class I or II	Yes−‡	Yes	Yes	Randomized double-blind	Fentanyl requirements*

[a] Patient symbols: ¢ = high anxiety; £ = low anxiety, § = no treatment, ¥ = other controls, † = perceived, • = subliminal.
[b] Initial sham control buzz = +, no initial sham buzz = —, and patient unconscious = ‡.
[c] Items with an asterisk indicate that they are used in the meta-analysis. Abbreviations used in table: POMS, Profile of Mood States; TMAS, Taylor Manifest Anxiety Score; Clin assess by psych, clinical assessment by psychiatrist of anxiety; BDI, Beck's Depression Inventory; STAI, State/Trait Anxiety Index; HSGHS, Scale of Hypnotic Susceptibility; HAS, Hamilton Anxiety Score; IPAT, Institute for Personality and Ability Testing; Zung, Zung's test; Spielberger, Spielberger Test; WAIS, Weschler Adult Intelligence Scale; Rev. β, Revised Beta; MMPI, Minnesota Multiphasic Personality Inventory; painful memory, memory of painful Kocker clamp application; SBP, systolic blood pressure; painful movement, movement with painful Kocker clamp application.

as to source and results before scoring items that might indicate the chances of distortion. A final score, the summation of satisfactory items divided by the total possible, was constructed on a scale of 0 to 100.

Outcome Measures

To identify available endpoint measures for pooling studies in an unbiased manner, we read the Methods section of each paper blinded to the results. Since CES is used to treat a wide range of conditions, there is a large diversity of endpoints, with only a few studies sharing a common endpoint measure, such as Hamilton Depression Scale score.

In our meta-analysis, we pooled studies only within each separate target indication. In pooling studies within each indication, we used only one outcome measure per study in order to give the studies nominally equal weight. If more than one outcome measure was available, we chose the measure that had the highest representation among the studies for that indication.

In conducting a meta-analysis for each target indication, we need to combine results across various outcome measures, as no outcome measure was common to all studies. In Table 1, we indicate the outcome measures we used to analyze the treatment of anxiety, brain dysfunction, insomnia, headache, and operative pain. For example, in the Anxiety section of Table 1, the meta-analysis combines one study using the scales of Profile of Mood States, one study using a clinical rating, three studies using the State/Trait Anxiety Index, and three studies using the Taylor Manifest Anxiety Score.

Effect Size Methodology

To combine different outcome measures within each indication, we use the statistical method of effect sizes (Glass et al., 1981). This method permits us to combine different outcome measures that reflect the same underlying concept. In this method, we standardize each difference between treated and placebo groups within each study before averaging across studies.

In the studies meta-analyzed in this paper, we compute the effect size as the difference of the differences. That is, we take the difference between the final and initial mean values for the experimental group, the difference between the final and initial mean values for the control group, and then the difference between the two. We then divide by the standard error of the control group differences to obtain the effect size. None of the studies presented the more accurate statistic, the mean and standard error of each patient's change. Independent of the units of the original measure, the resulting effect size will have a standard error of close to $2/N^{1/2}$, where N individuals were randomized between two treatments.

We apply the DerSimonian and Laird (1986) random effects model to compute an estimate of pooled effect sizes with confidence intervals. Since our aim is to perform a significance test of the hypothesis of no treatment difference, this effect size method provides a more powerful test than would an identical analysis on a necessarily smaller number of studies sharing identical outcomes.

A number of the studies did not report the standard errors or standard deviations that are needed by the DerSimonian and Laird models or did not report them in a consistent manner. This diversity makes it difficult to calculate effect sizes and standard errors. Rather than omit a study that does not provide this information, we used a variety of methods to estimate these parameters depending on the information that was provided by the authors.

To estimate the after minus before score variance, we assumed that the covariance of before and after was zero. This assumption results in larger variances of after minus before scores. Thus, our analysis will be more conservative than if the published studies had provided the correct standard deviations.

For the measures in the Anxiety section of Table 1, such as the Taylor Manifest Anxiety Score used in Moore et al. (1975), a higher measurement score reflects higher anxiety. Therefore, a positive effect size indicates increased anxiety, while a negative score indicates a reduction in anxiety. The results of the various effect size calculations are presented in Figures 1 through 4.

Table 1 lists 11 RCTs that compared CES to sham treatment of anxiety. Eight of the studies included sufficient data on continuous scales of anxiety to be included in the meta-analysis. The Marshall and Izard (1974) study provided insufficient data to allow estimation of an effect size. Two studies, by Hearst et al. (1974) and Tomsovic and Edwards (1973), provided nonstandard categorical data on levels of improvement, such as improved slightly or moderately. The Hearst study included only three patients with anxiety and so was excluded from further analysis. We dichotomized the results in Tomsovic and Edwards (1973) into proportion with no improvement to slightly improved and proportion moderately improved to complete remission.

We do not have a well-developed methodology at hand that would allow us to combine the eight studies with continuous scale measurements with the Tomsovic and Edwards (1973) study with categorical measurements. For this reason, we carry out the meta-analysis on the eight continuous variable studies and separately report the result of the Tomsovic and Edwards (1973) categorical data study.

Although we formally incorporated the data in the two papers by Smith (Smith and O'Neill, 1975; Smith, 1982) into our analysis, we note that their methods pose particular difficulties. Critical data are missing

and data selection that is incompletely defined and justified is included in both.

The DerSimonian-Laird model we used to compute pooled effect size estimates allows that the studies in the meta-analysis are a sample drawn from a heterogeneous universe of study populations. The method estimates this heterogeneity and includes it in estimates of variance which are therefore larger. For this reason, the model provides conservative estimates of pooled significance levels. However, if the data indicate little or no heterogeneity, then the model converges toward the homogeneous situation and the estimates are appropriate under homogeneity.

We use the version of the model that calculates pooled effect sizes for continuous variables, since in each of our analyses we use measures, such as anxiety scales, that are continuous. In the case of anxiety scales, we take the difference between the final and initial score. Since a lower score indicates improvement, we expect the effect measures to be negative when we observe improvement.

Results

Meta-Analyses of Effect Sizes for Efficacy of Treatment of Anxiety, Brain Dysfunction, Pain, and Insomnia

Figure 1 shows that improvement occurred in seven of the eight studies for anxiety that used continuous measurement scales. Figure 1 presents the results of the meta-analysis of the eight studies analyzing the efficacy of CES treatment for anxiety. Of the seven studies, only two (Ryan and Souheaver, 1976, and Schmitt et al., 1986) independently showed CES to be better than sham treatment ($p < .05$). The pooled point estimate for the eight studies is $-.5883$, with relatively narrow confidence bounds ($-.9503$, $-.2262$). The overall pooled result shows CES to be better than sham treatment at a statistically significant level ($p < .05$).

The Anxiety section of Table 1 shows that of the eight studies, five provided sham treatment in which the control group received an initial buzzing sensation similar to the CES-treated group. In a sensitivity analysis, we separately analyzed this subgroup of studies that used a more convincing sham treatment. Figure 1 shows the pooled point estimate for the five studies of $-.5374$ (-0.9939, $-.0808$), in favor of CES ($p < .05$).

A chi-square test for the categorical data in the Tomsovic study showed a nonsignificant trend in favor of sham treatment, with χ^2 ($1df$) = 1.685 (p = 1.45). We do not know precisely how the Tomsovic study, with its nonsignificant trend in favor of sham treatment, would affect the results of the meta-analysis of the eight studies using continuous scales.

Turning to CES treatment of brain dysfunction, the results presented in Figure 2 show no trend toward significance. Therefore, these two studies provide no indication that CES might prove fruitful for treatment of brain dysfunction.

Pooling the two individually positive studies on headache provides a very modest improvement of the confidence intervals (see Figure 3).

A meta-analysis of the Stanley et al. (1982a, 1982b) studies on the efficacy of CES in reducing anesthetic requirements (see the Insomnia section of Table 1) was not possible because the data presented did not permit the computation of standard deviations.

The meta-analysis of insomnia did not alter the negative appraisal of the two individual insomnia studies (see Figure 4).

Discussion

We grouped the accepted studies by indication treated: anxiety, brain dysfunction, headache, insomnia, and operative pain under anesthesia. Many studies included more than one outcome measure. To give the studies nominally equal weight in each meta-analysis, we selected one outcome from each study, picking the outcome measure that was used most frequently in the studies for that indication.

Although randomized assignment to treatments was

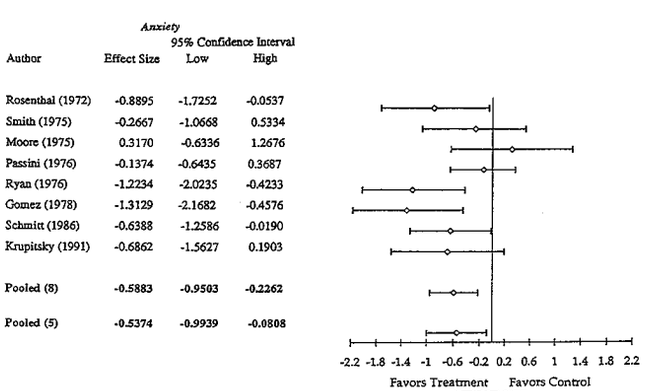

FIG. 1. Meta-analysis of RCTs of efficacy of CES treatment for anxiety. A negative change represents an improvement of CES over sham treatment.

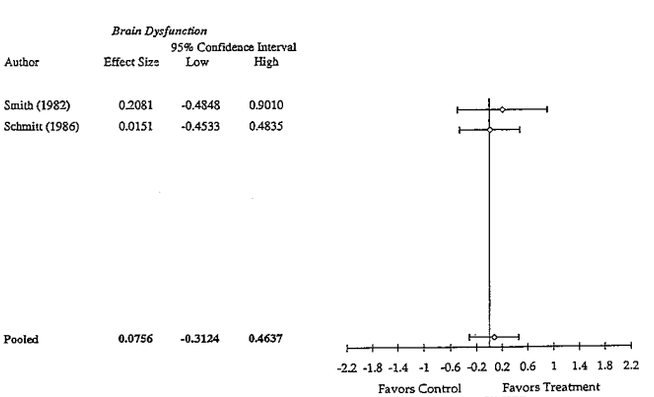

FIG. 2. Meta-analysis of RCTs of efficacy of CES treatment for brain dysfunction. A positive change indicates improvement.

a requirement for acceptance of a paper, we found that there were still defects in quality among the accepted papers that could limit the applicability of the results. Despite our efforts to identify high quality papers, the application of a previously developed method for assessing quality produced an average quality score for the 11 anxiety studies of .241 (on a scale of .0 to 1.0). This score is quite low compared with an average of .42 (SD = .16) obtained with the same method in a review of over 400 RCTs published since the 1950s (Reitman et al., 1987).

One of the chief flaws of the studies relates to blinding. Many authors characterized their randomized control studies as being double-blind, meaning that both the patient and the assessor were unaware of whether treatment was real or sham. However, with the exception of the Schmitt et al. (1984) and Hearst et al. (1974) studies, the therapist providing CES or sham CES was not blinded. We believe that this lack of blinding of the therapist poses potential bias, thereby making it difficult to interpret study outcomes. In addition, future publications should include a level of detail that would make it possible to update analyses such as those reported here.

Our review of the CES trial literature reveals the importance of providing certain basic information. Research results should include means, standard deviations, *N*s, statistical tests used and their *p*-values, standard deviations for paired before and after data, and ranges.

Baseline information used in the analysis should be for those subjects for whom complete follow-up data are available. If subjects with high anxiety are more likely to drop out, then the effect of intervention may be exaggerated. As an example, initial Hamilton anxiety scores of dropouts may be higher than scores of those who completed treatment. Therefore, the difference between initial and final scores may be spuriously greater if we include initial values for all patients who began treatment.

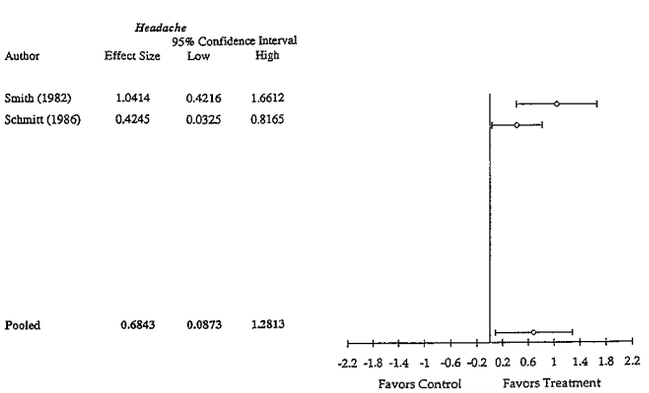

FIG. 3. Meta-analysis of RCTs of efficacy of CES treatment for headache. A negative change represents an improvement of CES over sham treatment.

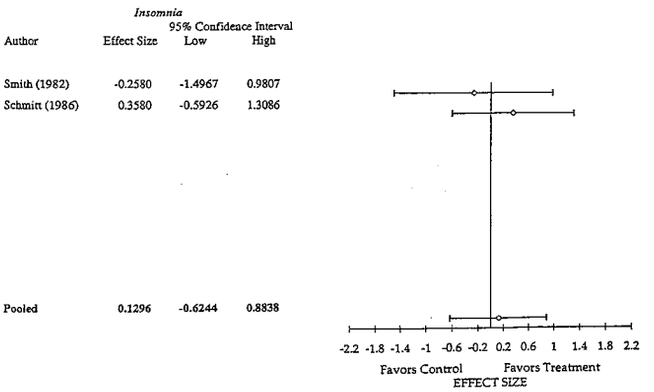

FIG. 4. Meta-analysis of RCTs of efficacy of CES treatment for insomnia. A negative change represents an improvement of CES over sham treatment.

In at least one study, we found that the authors conducted analyses of data using methods not specified in advance. This practice raises the possibility of bias and weakens the overall rigor and credibility that the authors presumably hope to attain. Since at least several of the published studies were conducted by individuals with a commercial interest in a specific CES device, we are also concerned with the possible bias those interests might introduce. We suggest that such advocates might more fruitfully sponsor evaluations by independent research groups to increase the credibility of results.

We meta-analytically pooled study results within each indication, in order to increase our power to detect effects of therapy. We used the DerSimonian and Laird (1986) random effects model to take into account the heterogeneity of the studies. For technical statistical reasons, we were not able to pool the two studies on the use of CES to reduce the anesthetic requirement for operative pain.

In many of the studies, the sham-treated group experienced improvement. This observation appears to warrant further investigation regarding the potentially strong placebo effect of CES apparatus and protocols, independent of current.

The analyses performed are limited by the small number of studies for any specific indication, by the small number of patients randomized within each study, and by the methodological and design problems we have identified here.

A related concern is the "file drawer" problem—the fact that negative results are less likely to be published than positive ones. Whenever the pooling of randomized controlled trials results in a *p*-value close to .05, the possibility of publication bias raises its ugly head (Dickersin, 1990; Dickersin et al., 1992). A few less significant studies residing in investigators file drawers could diminish enthusiasm about the published sample. This possibility calls for caution in the interpretation of results that are barely statistically significant.

Conclusion

The notable result arising from the meta-analysis of studies for each of four indications was that the pooled result for the eight studies analyzing the treatment of anxiety with continuous scales was in favor of CES at a statistically significant level (effect size estimate = −.5883; 95% confidence interval = −.9503, −.2262). The result in favor of CES remained significant when we dropped the three studies that provided no convincing sensation in their sham protocol.

Pooling the two independently positive studies on headache yielded a positive effect size of .6843 with confidence interval (.0872, 1.2813). Pooling did not alter results of studies that were independently negative (brain dysfunction, insomnia, and headache). Studies on pain under anesthetic were independently positive and were not pooled for technical statistical reasons.

Only the two Schmitt studies blinded the CES therapist, so that all other studies are subject to potential bias. To avoid this potential for bias, we strongly recommend that all future studies blind the therapist by the use of a preset circuit.

The potential for bias also arises from post hoc subgroup analyses within individual studies that were not planned before the review of the outcome data. We strongly urge researchers to adhere to protocols devised prior to conducting studies in order to avoid this problem.

We also urge those having a direct commercial interest to sponsor effectiveness research by an independent third party. This arrangement might best serve the long-term interests of the advocates by ruling out questions of real or perceived bias.

The conclusions reached in this study must necessarily be confirmed by larger, rigorously controlled studies.

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