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# Effects of Cerebral Electrical Stimulation on Alcoholism: A Pilot Study

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**Cerebral electrical stimulation (CES), born from research on electroanesthesia in the seventies, consists of the application of a pulsating current of small intensity (usually less than 1 mA, and below the threshold of perception) through the skull, e.g., in daily 30-min sessions.**

**Claims of biological effectiveness (neurochemical, hormonal and EEG changes, naloxone-reversible analgesia in rats, etc.) and of clinical effectiveness (anxiety, depression, cognitive functions in alcoholics) have often relied on poorly controlled data. A recent controlled study in the treatment of opiate withdrawal has been positive. The present double-blind controlled study compares active CES with sham stimulation in 64 alcohol-dependent males. Over 4 weeks, both treatment groups improved significantly in most aspects. In the active treatment group additional significant improvement was observed in week-end alcohol consumption, and in two psychological measures: depression and stress symptoms index, but not in general drinking behavior.**

**Key Words: Alcohol Consumption, Cerebral Electrical Stimulation, Psychological Measures, Craving, Controlled Clinical Trial.**

THE DEVELOPMENT OF psychopharmacological treatments in alcohol dependence has been recently the object of several comprehensive reviews.[1–3] They include for instance inhibitors of serotonin re-uptake,[4] dopamine agonists,[5–7] GABA agonists.[8] Even if any of these experimental psychopharmacological approaches prove clinically helpful, they would meet serious obstacles in practice, such as problems with compliance; resistance to any pharmacotherapy in alcoholics by some members of the influential Alcoholics Anonymous, and finally, possibilities of dangerous interactions between the proposed drugs and alcohol. Therefore, a nonpharmacological adjunct, such as cerebral electrical stimulation (CES), may be easier to integrate with existing psychological and social approaches.

CES was born from research on electroanaesthesia (electrosleep) in the 1960s and 1970s.[9–11] It was noted that some subjects undergoing this procedure exhibited favorable changes in mood. The technique of CES is variable but involves a number of common denominators.[10,12,13] Typically, a battery source is used to supply a pulsating constant current (20–200 Hz, maximum amplitude up to 20 mA, but usually <1 mA, often containing a DC component or a charge compensation phase) through the skull via two to four surface electrodes; the usual direction of current is fronto-occipital, although other arrangements have been tried.

In *studies on animals* CES has been found to cause a naloxone-reversible analgesia in rats, suggesting that CES may release endogenous substances in brain, such as endorphins or serotonin.[14–17]

*Studies of biological correlates in human* have allegedly identified a potential field caused by CES sufficient enough to elicit physiological responses of neurons recorded in hippocampus with implanted electrodes.[18]

*Human clinical studies* have claimed: a favorable influence on anxiety and depression[19–22] in psychiatric patients; improvement of cognitive dysfunctions in alcoholics;[10,23] an improvement in anxiety and depression in clinically drug dependent individuals, although not specifically in alcoholics.[10,12,21,22,24,25]

There are methodological problems with many of these studies which appear more optimistic than well controlled.[26] They are often poorly designed, have unclear dependent variables, and/or have confusing treatment outcomes. An uncontrolled study of 400 narcotic addicts[27,28] claimed that CES reduced craving and eased the withdrawal from narcotic abuse, although this finding was questioned.[29] In a more recent double-blind placebo-controlled experiment, CES effectively alleviated symptoms of opiate withdrawal.[30]

To our knowledge, none of the studies on CES effects have attempted to measure its influence on drinking behavior per se, i.e., craving and/or alcohol consumption. Therefore, the first objective of this work was to assess the possible effect of CES on drinking behavior. In addition, it seemed appropriate to examine the effects of CES on psychiatric symptoms secondary to alcohol abuse, because anxiety, depression, and decreased tolerance to stress are major symptoms of primary alcoholism. Results of these studies were communicated in a preliminary form.[31] An independent study of CES effects on the cocaine withdrawal syndrome is in progress and will be reported separately.

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## METHODS

### *Determination of Sample Size*

In previous clinical trials with ambulatory alcoholics of similar severity, we have observed a 20% attrition over the initial 4-week period. A power analysis was conducted based on a pilot study of 30 subjects. We set as a goal to detect 20% difference in improvement following active stimulation over sham treatment, in dependent variables (using a 2-tailed test) at the 5% level of significance with a power of 80%. Depending on the outcome variables of interest, this calculation provides $n$ of between 15 (e.g., for symptoms of depression) and 75 (e.g., for craving) completing subjects in each group (CES and control). As a comparison, published results of studies assessing the effect of pharmacological agents on alcohol consumption[32] used sample sizes at the lower end of this range.

### *Recruitment and Selection of Subjects*

Advertisements in the media led to an initial selection after a 20- to 30-min interview on the telephone. Subjects had to express a motivation to decrease alcohol intake or abstain from it, but abstinence was not a required goal.

### *Inclusion Criteria*

DSM-III-R criteria for alcohol dependence;[33]

Duration of alcohol abuse for more than 6 months;

Sex: males only, to avoid the complications of dealing with hormonal cycle;

Age: limited to between 25 and 60 years (younger alcoholics include a high proportion of antisocial personalities, leading to an increased attrition rate; older than 60 have too frequent cognitive impairments);

Primary dependence (exclusion of any pre-existing psychopathology, including antisocial personality disorder, borderline personality disorder, psychosis, major depression). DSM-III-R criteria were used for the definition of these conditions;

Drinking quantity and frequency: at least 6 units per day (units = "standard drinks" related to body weight, i.e., 13.6 g of absolute ethanol for a 70 kg person) and at least 4 drinking days per week;

Subjects willing to attend 30-min daily cerebral electrotherapy stimulation sessions from Monday through Friday;

Informed consent was obtained from every individual subject; they were also informed of double-blind randomization procedure and random allocation to treatment.

### *Exclusion Criteria*

Intermittent alcoholism: the subjects should not have been able to abstain for three periods of at least 2 months over the past 3 years;

Medical or surgical problems requiring continuous or immediate treatment or requiring a prescription drug on a regular basis. Advanced liver damage, incompatible with ambulatory treatment, was of course a cause of exclusion. Actually, no candidate was refused on this basis.

Associated current drug addiction (DSM-III-R criteria for drug dependence) including prescription drugs;

Distance from hospital of such a nature as to make daily attendance to the sessions doubtful.

### *Experimental Treatment*

CES was administered 5 days a week, Monday through Friday, for 30 min between 5:00 and 8:00 p.m., by trained technicians. Practical considerations precluded 7-day treatment. Subjects were lying down in isolation and silence.

The wave form produced by the stimulator (N-S, Inc.) consists of a carrier wave (modified square wave) of 20 kHz modulated by low frequency pulses of 100 Hz at 50% duty cycle. The stimulator includes a built-in sensor for impedance of electrical contact, which automatically turns off the applied current if there is a short circuit or if excessive current is passed or if contact is not complete. One should therefore expect that the CES using our stimulator should incur the same or lower rate of side effects compared with experience with other similar devices.

Six hand-held stimulators were used in this study; three were wired to provide correct current flow, and three were arranged for a sham treatment (see below). They were indistinguishable and labeled by letters. A randomization table was used to allocate a particular stimulator to subjects; the stimulator remained the same throughout 4 weeks of treatment. Electrodes (standard, self-sticking, nonirritant gel, disposable TENS electrodes, surface area 1 $cm^2$, from Vermont Medical, Inc., applied to the skin cleaned with alcohol) were placed as follows: two frontal (6 cm separation), two on each mastoid.

In the treatment group, the current flow was between the frontal and mastoid electrodes. In the sham group, the current was arranged to flow between the adjacent frontal electrodes, so that the stimulation was limited to the frontal skin and there was no transcranial current flow. This procedure was selected rather than a complete absence of current to better maintain the blindness of subjects and therapists for the actual treatment assignment (see below).

Previous practice of CES was based on the use of sub-threshold levels of stimulation.[10,34] To secure this parameter in our study, an individual threshold determination was performed on each subject using method of limits and signal detection procedures.[35] A separate setup was developed to perform these tests, consisting of a CES machine in which pulse protocols were controlled by a computer (IBM-PC type) with automatic registration of subjects' answers. The treatment used current intensity 10% sub-threshold for each patient. Despite this procedure CES was sometimes perceived by the subject as warmth or mild tingling and for that reason we have chosen the type of sham treatment described above. However, in the protocol that follows the present pilot study, a control group without current application is also included to control any possible effect of current stimulation through the skin.

### *Assessment Techniques*

Sociodemographic characteristics of subjects were obtained in initial interview.

Measures of efficacy of CES treatment were: Initial and final assessments were based on a battery of instruments, well established in the measurement of psychopathology, on one hand, and of drinking behavior, on the other.

1. Psychopathological inventory: depression scales (Hamilton Depression Scale,[36] Montgomery-Asberg Scale[37]), anxiety scale (Hamilton Anxiety Scale[38]), and the Symptom Check List (SCL-90-R[39]);

2. Drinking behavior assessment: Drinking behavior inventory (DBI[40]); Michigan Alcohol Screening Test (MAST[41]); Alcohol Dependence Scale (ADS[42]); Alcohol consumption (daily quantity and frequency assessment), and intensity of craving.

Daily self-monitoring of alcohol consumption was obtained during the week preceding the onset of treatment (defined as baseline consumption) and continued throughout the study, using an ad-hoc form. Variations of alcohol intake were assessed in terms of number of standard drinks consumed daily (see above, Methods Section 3) and number of drinking days. Although the validity of self-report of alcohol consumption is questioned,[43] a majority of authors consider them as valid.[44–47] We have cross-checked self report with daily saliva test for alcohol (Alcoscreen, Chem-Elec, Inc., North Webster, IN), applied before daily treatment and by measuring liver enzymes (gamma-glutamyltransferase - GGT, SGOT, SGPT).

An analogue measure of craving was obtained every day during the treatment (subject was asked to mark a pencil trait on a 10-cm line from zero to maximum desire to drink alcohol).

Adverse reactions record. One of the characteristics of the CES is its apparent safety and lack of any side effects, except for 1–2% occurrence of mild headaches[10]). However, we have systematically collected information on possible adverse reactions using a symptom checklist and an Adverse Events Record, which is an open-ended questionnaire. This

**Table 1.** Characteristics of the Population

| Characteristics | Active $n = 28$ | | Sham $n = 34$ | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $p^*$ |
| Age | 40.18 | 9.76 | 39.97 | 10.36 | 0.94 |
| Income group | 5.15 | 2.80 | 5.97 | 2.69 | 0.26 |
| Years of education | 13.93 | 3.83 | 13.44 | 3.30 | 0.59 |
| Baseline alcohol consumption | 10.46 | 5.23 | 12.99 | 6.96 | 0.11 |
| Years of alcohol abuse | 9.68 | 7.75 | 12.29 | 9.81 | 0.26 |
| Alcohol abuse (days/week) | 6.32 | 0.98 | 6.09 | 1.33 | 0.45 |
| MAST | 25.75 | 9.82 | 26.29 | 8.48 | 0.82 |
| ADS | 17.00 | 6.24 | 17.44 | 6.32 | 0.78 |
| DBI | 46.82 | 20.03 | 51.56 | 24.60 | 0.42 |
| GGT | 81.04 | 86.68 | 78.67 | 91.36 | 0.92 |
| MCV | 96.25 | 3.88 | 95.27 | 5.55 | 0.43 |
| SCL-90R: | | | | | |
| Depression | 1.41 | 0.71 | 1.29 | 0.71 | 0.49 |
| Anxiety | 1.08 | 0.86 | 1.05 | 0.79 | 0.90 |
| PST | 51.43 | 20.79 | 49.91 | 18.01 | 0.76 |
| GSI | 1.02 | 0.62 | 1.00 | 0.61 | 0.92 |
| PSDL | 1.65 | 0.49 | 1.69 | 0.50 | 0.75 |
| Hamilton Depression Scale | 19.61 | 7.70 | 19.82 | 7.45 | 0.91 |
| Hamilton Anxiety Scale | 15.11 | 8.02 | 16.21 | 8.93 | 0.62 |
| Mini Mental Status | 37.82 | 6.74 | 36.79 | 7.74 | 0.58 |
| Current intensity | 592.86 | 379.99 | 544.12 | 266.22 | 0.56 |

* $p$ = significance of independent samples $t$ tests.

questionnaire was administered weekly during the 4 weeks of treatment. Emergency admission to an inpatient detoxification program for alcoholics was available (as well as benzodiazepines on a PRN basis) in case of severe withdrawal symptoms, but were never used or required.

Medical symptoms inventory and physical examination, using ad hoc forms.

Biological tests. A battery of tests was administered at the intake and at the end of the study (blood: Hgb, Hct, RBC, WBC and differential smear, ESR, protein, B12, folate (RBC and serum), T3 (FIA), T4, T5 uptake, SGOT, SGPT, GGT, direct and indirect bilirubin, alkaline phosphatase, albumin, globulin, electrolytes including Mg, PO4, VDRL, BUN, creatinine, serum choline; urine: routine urinalysis).

### *Ethical Considerations*

All subjects participating in the study signed a consent form and were informed of the existence of randomized allocation into active or sham treatment groups. The experimental protocol was approved by the Ethics Committee of the Douglas Hospital Research Centre.

### *Data Analyses*

The primary endpoints were changes in drinking behavior and psychopathology between baseline and the end of treatment. The analysis of all variables, in global and in subscores whenever applicable, was done in two steps:

1. Paired $t$ test comparing the baseline scores with the end scores within each treatment group to evaluate the change.

2. Independent samples $t$ test was used to compare degrees of improvement (change score = end score − baseline score) in dependent variables to assess the effectiveness of active treatment in comparison with the sham treatment group.

The repeated measure of ANOVA was used for alcohol consumption, sleeping hours, and measures of craving. We also applied the Greenhouse-Geisser correction; this approach makes the ANOVA univariate hypotheses more conservative (by not rejecting null hypotheses as it should be done otherwise, see pp. 523–524 in Winer[48]).

All calculations were done using SPSS-PC+ statistical package on an i286-based computer. Data were considered significant at $p < 0.05$.

## RESULTS

### *Characteristics of the Population*

The baseline measures of randomized subjects are shown in Table 1. The two groups (sham: 34; active: 28) were well matched with respect to the sociodemographic data and age, drinking behavior, and psychopathology, although there was a nonsignificant difference in baseline alcohol consumption in years of alcohol abuse (25% higher in the sham group). Also, average current intensity, determined on the basis of threshold study (see Methods), was equivalent in both groups. These results demonstrate that the randomization process was largely successful and that at entry into the study the two groups could be considered as being essentially equivalent. In addition, it should be stressed that the various scales of alcohol abuse and dependence (MAST, ADS, DBI) show that this population suffers from serious alcohol dependence and is clearly more dependent than the "heavy drinker" category. Of 67 subjects recruited at the beginning of the study, five dropped out, all from the active treatment group. The baseline data of dropouts were not significantly different from completers.

At the end of the treatment, before the opening of the code, the therapists, assessors and subjects were asked to guess the subject's assignment. There was no correlation between their guesses and the actual allocation showing that the blindness of all concerned was well maintained.

### *Changes in the Dependent Variables*

Based on our working hypothesis, we analyzed two categories of variables: those related to alcohol consumption, and those related to associated psychopathology.

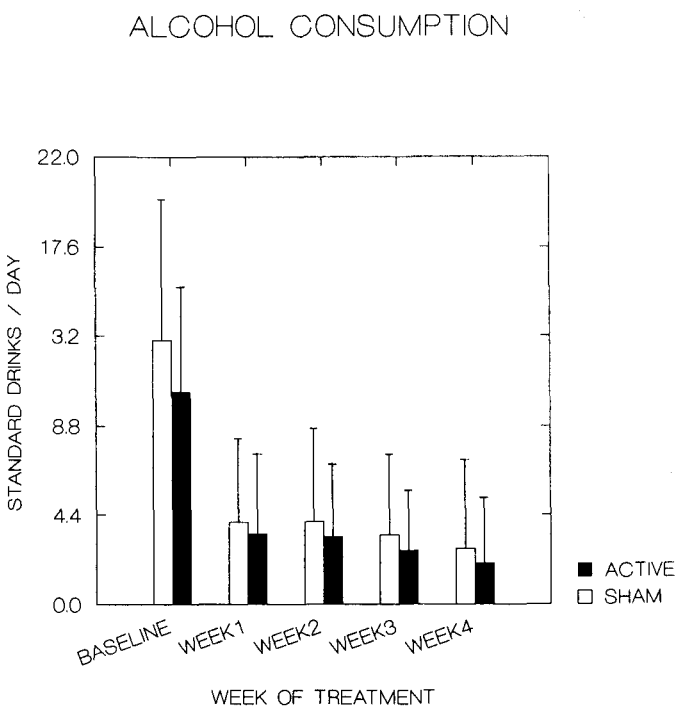


**Fig. 1.** Comparison of alcohol consumption, expressed in standard drinks per day, at different times in trial.

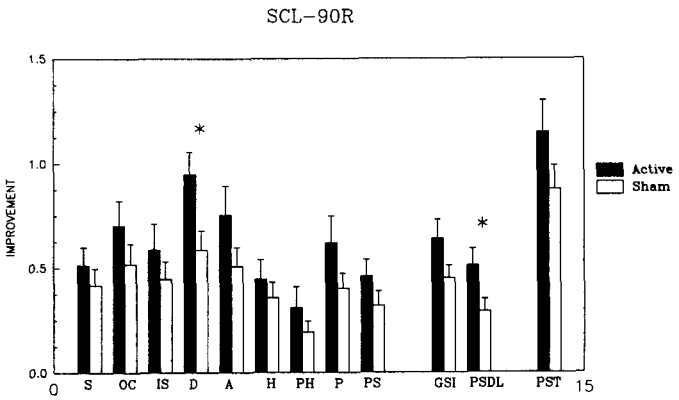


**Fig. 2.** Comparison of improvement in SCL-90R scores at the end of 4 weeks of CES between the active and sham treatment groups. Improvements in subscores for depression and positive symptoms distress level are significantly different (by $p < 0.05$ by independent samples $t$ test) although all subscores show trend of improvement in favor of active treatment. S, somatization; OC, obsessive-compulsive; IS, interpersonal sensitivity; D, depression; A, anxiety; H, hostility; PH, phobic anxiety; P, paranoid ideation; PS, psychoticism; GSI, general symptomatic index; PSDL, positive symptoms distress level; PST, positive symptoms total. Ordinate for PST is 1/20 of the scale.

*Alcohol Consumption.* The alcohol consumption in both the active and the sham treatment groups significantly decreased during the 4 weeks of intervention ($F = 3.21$, $df = 2, p = 0.044$). Fig. 1 illustrates this "study effect", i.e., the favorable influence of making the decision to enter the study, undergoing detailed assessment of drinking behavior and its consequences, daily monitoring alcohol consumption, establishing a daily relationship with therapists, etc. However, the difference in alcohol consumption between the treatment groups was not statistically significant ($F = 0.07$, $df = 2, p = 0.937$).

The results of self report were in agreement with the saliva alcohol test in all but a few instances (<0.5%). There was no statistical difference between the treatment groups in the proportion of subjects who were able to reach abstinence during the trial (active: 22.22%; sham = 18.18%; Chi-square = 0.15, $p = 0.7$).

More detailed analysis of daily alcohol consumption revealed an unexpected pattern characterized by a higher weekend consumption in the sham but not in the active treatment group (Fig. 2). This difference was statistically significant when analyzed with the appropriate repeated measure ANOVA ($F = 3.21$, $df = 2, p = 0.04$; see also Table 2). Because this is a post hoc finding, we do not have baseline control for these patterns (i.e., only the global weekly consumption is available).

We were able to obtain follow-up data on consumption from 21 subjects in the active treatment group and 22 from the sham treatment group 6 months after termination of the treatment. Both groups consumed significantly less alcohol than at the baseline but the difference between the study groups was not statistically significant.

*Psychopathology.* The changes in associated psychopathology in both study groups, as measured by SCL-90-R, were comparable. Both the active and the sham groups improved significantly on all subscales and global scores of the scale during the 4 weeks of intervention (for all measures $p = 0.001$, cf. Fig. 3).

There was a general trend toward greater improvement (end score − baseline) in the active treatment group as compared with the sham, but only in the depression subscale the difference between the groups reached the level of significance ($t = -2.56$, $df = 60$, $p = 0.013$, Fig. 3). This trend contributed to the significantly higher improvement in the global measure of psychopathology of SCL-90-R, the positive symptoms distress level ($t = -2.09$, $df = 60, p = 0.04$).

*Other Measures.* No significant differences were found between the groups in measures of craving, number of drinking days, sleeping hours, and GGT plasma levels.

We have done some preliminary studies measuring beta-endorphin in subjects undergoing CES. In an open study on 19 subjects, we have found a significant increase in beta-endorphin at the end of 4 weeks of CES (baseline before treatment: 80 ± 62 pg/ml serum; after 4 weeks of CES: 273 ± 167, mean ± SD, $p < 0.05$).

## DISCUSSION

CES cannot be considered as an established method either in psychiatry or in somatic diseases. However, in the field of substance abuse, several controlled studies of the effects of CES have been conducted with some encouraging results. We are not aware of any study, however, on its effectiveness on actual drinking behavior and alcohol con-

**Table 2.** Analysis of Alcohol Consumption Factors of Repeated Measure ANOVA*

| Source of variation | SS | DF | MS | *F* | *p* |
|---|---|---|---|---|---|
| Time factor | | | | | |
| Within cells | 691.26 | 120 | 5.76 | | |
| B | 36.94 | 2 | 18.47 | 3.21 | 0.044† |
| A×B | 0.75 | 2 | 0.38 | 0.07 | 0.937 |
| Weekend/weekdays condition | | | | | |
| Within cells | 402.50 | 60 | 6.71 | | |
| C | 44.78 | 1 | 44.78 | 6.68 | 0.012 |
| A×C | 29.67 | 1 | 29.67 | 4.42 | 0.04 |

* Abbreviations: SS, sum of squares; DF, degrees of freedom; MS, mean squares.
† After Greenhouse-Geisser conservative correction, $p = 0.05$ (Winer, 1971).

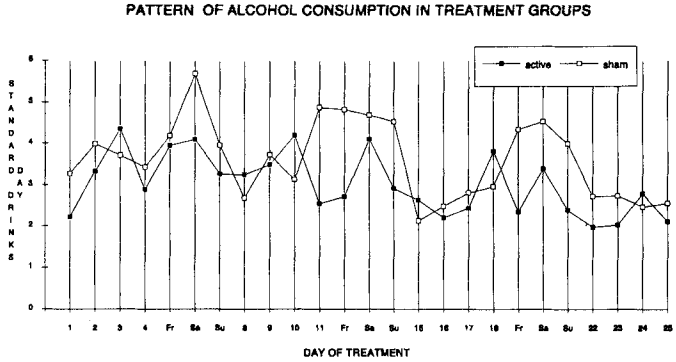


**Fig. 3.** Comparison of alcohol consumption, expressed in standard drinks per day, on weekdays (average for Monday–Thursday) versus weekends (average for Friday–Sunday) for each week of the CES treatment (see also Table 2 and Methods for details).

sumption. The present pilot study provides evidence that CES affects several concomitants of alcohol abuse, although the clinical significance of this finding remains to be established.

The influence of CES on actual alcohol consumption is obviously weak, as it is reduced significantly only during the weekends. Furthermore, the pattern of drinking (i.e., higher on weekend than on weekdays) was a serendipitous finding at the stage of data analysis. At present we do not know of any associated behavioral changes that might explain these results. Whether the effect of CES on alcohol consumption is primary or secondary to the significant improvement of stress symptoms, mood, and in particular depression, is an open question.

An additional caveat has to be expressed regarding the generalizability of our findings. Besides our rather narrow inclusion criteria, it is obviously a special subgroup of alcoholics that muster the motivation to answer an advertisement, enter a double-blind placebo controlled study, and follow it 5 days/week for 4 weeks.

It is worth mentioning that the changes in associated psychopathology in both treatment groups, as measured by SCL-90-R are comparable in terms of magnitude to placebo-controlled pharmacological trials conducted in similar populations in our alcohol research clinic.[6,49,50]

CES appears to have almost immediate effect (see Fig. 3): during the first weekend, after 5 days of treatment, the consumption is already significantly reduced, albeit intermittently (i.e., during weekends only).

As mentioned earlier, our results indicate that the randomization of subjects was satisfactory as evidenced by a lack of significant difference between the active and the sham groups in terms of population characteristics. In view of the polymorphous nature of alcoholism, this point is of special importance in any clinical research in the field.

The subjects were generally suffering from serious consequences of alcohol abuse as evidenced by baseline data (Table 1). They differ markedly in that respect from the drinkers described in recent psychopharmacological trials, e.g., on the effects of zimelidine[32] and citalopram[4] (drugs enhancing serotoninergic transmission) as "nondepressed, socially stable, physically and emotionally healthy [. . .] with no history of depression or other psychiatric disturbance and who reported drinking an average of 28 standard drinks per week."

For the moment, the only clues as to the mechanisms of action of CES come from recent studies in animal models (see Introduction) which draw attention to the release of endogenous opiates.[14,16,17] Low levels of endorphins have been observed repeatedly in alcoholics, prompting some authors to propose an endorphin deficiency hypothesis in alcohol abuse.[51,52] Our preliminary results indicate that 1 month of CES might influence this mechanism.

Our preliminary follow-up studies show a significant decrease in alcohol consumption 6 months after the end of treatment, in comparison with the baseline consumption, for the two groups, with a trend for lower consumption in the active treatment group.

The trends observed in most of the dependent variables, in addition to those that have reached the threshold of significance, obviously encourage gathering additional data on a larger group of subjects to verify that the positive findings were not a consequence of multiple comparisons.

If further studies confirm a clinical usefulness of CES, at least for a subset of alcoholics, the treatment would compete with other biological methods, such as the use of psychopharmacological agents. For instance, Kissin[53] has advocated the use of chlordiazepoxide in assisting alcoholics in coping with the effects of protracted abstinence. He alluded to the three optimal qualities for a tranquilizing drug: 1) It should be effective in maintaining individuals in treatment; 2) it should have low potential for abuse; and 3) it should not potentiate the effects of alcohol. Whereas the

use of benzodiazepines in the treatment of alcoholism does not meet criteria 2 and 3, CES obviously would be in a position to meet all three criteria. In addition, the lack of side effects of CES would have to be taken into account.

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## REFERENCES

1. Liskow BI, Goodwin DW: Pharmacological treatment of alcohol intoxication, withdrawal and dependence: A critical review. J Stud Alcohol 48:356–370, 1987

2. Meyer RE: Prospects for a rational pharmacotherapy of alcoholism. J Clin Psychiatry 50:403–412, 1989

3. Sinclair JD: The feasibility of effective psychopharmacological treatments for alcoholism. Br J Addict 82:1213–1223, 1987

4. Naranjo CA, Sellers EM, Sullivan JT, Woodley DV, Kadlec K, Sykora K: The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther 41:266–274, 1987

5. Borg V: Bromocriptine in the prevention of alcohol abuse. Acta Psychiatr Scand 68:100–110, 1983

6. Dongier M, Schwartz G: The feasibility of effective psychopharmacological treatments for alcoholism [letter]. Br J Addict 84:227–228, 1989

7. Borg V, Weinholdt T: Bromocriptine in the treatment of the alcohol withdrawal syndrome. Acta Psychiatr Scand 65:101–111, 1982

8. Lhuintre JP, Daoust M, Moore ND, Chrétien P, Saligaut C, Tran G, Boismare E, *et al*: Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1:1014–1016, 1985

9. Limoge A. An introduction to electro anesthesia. Baltimore, University Park Press, 1975

10. Smith RB: Cranial electrotherapy stimulation, in Myklebust JB, Cusick JF, Sances, Jr., Larson SJ (eds): Neural Stimulation, vol. 2. Boca Raton, CRC Press, 1985, pp 129–150

11. Smith RB, O'Neil L: Electrosleep in the management of alcoholism. Biol Psychiatry 10:675–680, 1975

12. Jarzembski WB: Electrical stimulation and substance abuse treatment. Neurobehav Toxicol Teratol 7:119–123, 1985

13. Brown CC: Electroanesthesia and electrosleep. Am Psychol 402–410, 1975

14. Wilson OB, Hamilton RF, Warner RL, Johnston CM, DeFriece R, Harter L, Schweitzer C, et al: The influence of electrical variables on analgesia produced by low current transcranial electrostimulation of rats. Anesth Analg 68:673–681, 1989

15. Malin DH, Lake JR, Hamilton RF, Skolnick MH: Augmented analgesic effects of enkephalinase inhibitors combined with transcranial electrostimulation. Life Sci 44:1371–1376, 1989

16. Malin DH, Murray JB, Crucian GP, Schweitzer FC, Cook RE, Skolnick MH: Auricular microelectrostimulation: Naloxone-reversible attenuation of opiate abstinence syndrome. Biol Psychiatry 24:886–890, 1988

17. Qiao JT, Skolnick M, Dafny N: Dorsal raphe and external electrical stimulation modulate noxious input to single neurons in nucleus parafascicularis thalami. Brain Res Bull 21:671–675, 1988

18. Dymond AM: Intracerebral current levels in man during electrosleep therapy. Biol Psychiatry 10:101–104, 1975

19. Ryan JJ, Souheaver GT: Effects of transcerebral electrotherapy (electrosleep) on state anxiety according to suggestibility levels. Biol Psychiatry 11:233–237, 1976

20. Singh B, China G, Anand M, Bopari M, Neki J: Sleep and consciousness mechanisms with special reference to electrosleep. Armed Forces Med J India 27:292, 1971

21. Philip P, Demotes-Mainard J, Bourgeois M, Vincent JD: Efficiency of transcranial electrostimulation on anxiety and insomnia symptoms during a washout period in depressed patients: A double-blind study. Biol Psychiatry 29:451–456, 1991

22. Krupitsky EM, Burakov AM, Karandashova GF, Katsnelson JS, Lebedev VP, Grinenko AJ, Borodkin JS: The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. Drug Alcohol Depend 27:1–6, 1991

23. Smith RB, Day E: The effects of cerebral electrotherapy on short-term memory impairment in alcoholic patients. Int J Addict 12:575–582, 1977

24. Schmitt R, Capo T, Boyd R: Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. Alcohol Clin Exp Res 10:158–160, 1986

25. Patterson MA, Firth J, Gardiner R: Treatment of drug alcohol and nicotine addiction by neuroelectric therapy: Analysis of results over 7 years. J Bioelectricity 3:193–221, 1984

26. Alling FA, Johnson BD, Elmoghazy E: Cranial electrostimulation (CES) use in the detoxification of opiate-dependent patients. [Review]. J Subst Abuse Treat 7:173–180, 1990

27. Bourgeois M, Tignol J, Daubech J-F, Danlouede J-P, Allison W, Allison F, de Saint-Affrique H, et al: Sevrage des toxicomanies aux opiacés par électrothérapie du type Limoge. Bilan de 400 cures. Ann Med Psychol 140:540–546, 1982

28. Bourgeois M, Tignol J, Daubech J-F, Danlouede J-P, Yesavage J: Analgesic electrical self-stimulation in narcotics withdrawal. J Clin Psychiatry 44:317, 1983

29. Gossop M, Bradley B, Strang J, Connell P: The clinical effectiveness of electrostimulation vs oral methadone in managing opiate withdrawal. Br J Psychiatry 144:203–208, 1984

30. Ellison F, Ellison W, Danlouede J-P, Daubech J-F, Pautrizel B, Bourgeois M, Tignol J: Opiate withdrawal and electro-stimulation. Double blind experiments. Encephale 13:225–229, 1987

31. Padjen AL, Dongier M, Malec T: Cerebral electrical stimulation in the treatment of alcohol withdrawal and dependence. Alcohol Clin Exp Res 13:261, 1990

32. Naranjo CA, Sellers EM, Roach CA, Woodley DV, Sanchez-Craig M, Sykora K: Zimelidine induced variations in alcohol intake by nondepressed heavy drinkers. Clin Pharmacol Ther 35:374–381, 1984

33. American Psychiatric Association: DSM-III, Diagnostic and statistical manual of mental disorders, 3rd edition revised. 3rd ed. Washington, D.C., The American Psychiatric Association, 1987

34. Schmitt R, Capo T, Frazier H, Boren D: Cranial electrotherapy stimulation treatment of cognitive brain dysfunction in chemical dependence. J Clin Psychiatry 45:60–63, 1984

35. Falmagne JC: Elements of psychophysical theory. Oxford, Clarendon Press, 1985

36. Hamilton M: Standardized assessment and recording of depressive symptoms. Psychiat Neurol Neurochir 72:201–205, 1969

37. Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389, 1979

38. Hamilton M: The assessment of anxiety states by ratings. Br J Med Psychol 32:50–55, 1959

39. Derogatis LR, Rickels K, Rock A: The SCL-90 and the MMPI: A step in the validation of a new self-report scale. Br J Psychiatry 128:280–289, 1976

40. Shelton J, Hollister LE, Gocka ET: The Drinking Behavior Interview (an attempt to quantify alcoholic impairment). Dis Nerv Sys 30:464–467, 1969

41. Seizer ML: The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. Am J Psychiatry 1127:1653–1658, 1971

42. Skinner HA, Horn JL: Alcohol Dependence Scale User's Guide. Toronto, Addiction Research Foundation, 1984

43. Fuller RK, Lee KK, Gordis E: Validity of self-report in alcoholism

research: Results of a veterans administration cooperative study. Alcohol Clin Exp Res 12:201–205, 1988

44. Hesselbrock M, Babor TF, Hesselbrock V, Meyer RE, Workman K: "Never believe an alcoholic"? On the validity of self-report measures of alcohol dependence and related constructs. Int J Addict 18:593–609, 1983

45. Polich J: On the clinical application of P300. Biol Psychiatry 31: 647–649, 1992

46. Sobell LC, Sobell MB, Riley DM, Schuller R, Pavan DS, Cancilla A, Klajner F, et al: The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. J Stud Alcohol 49:225–232, 1988

47. Midanik LT: Validity of self-reported alcohol use: A literature review and assessment. Br J Addict 83:1019–1029, 1988

48. Winer BJ: Statistical principles in experimental design, 2nd ed. New York, McGraw-Hill, 1971

49. Dongier M, Vachon L, Schwartz G: Bromocriptine in the treatment of chronic alcoholism. Alcohol Clin Exp Res 13:283, 1990

50. Dongier M, Vachon L, Schwartz G: Bromocriptine in the treatment of alcohol dependence. Alcohol Clin Exp Res 15:970–977, 1991

51. Facchinetti F, Petraglia F, Nappi G, Martignoni E, Sinforiani E, Bono G, Genazzani AR: Functional opioid activity variates according to the different fashion of alcohol abuse. Subst Alcohol Actions Misuse 5:281–291, 1985

52. Blum K, Topel H: Opioid peptides and alcoholism: Genetic deficiency and chemical management. Funct Neurol 1:71–83, 1986

53. Kissin B: The use of psychoactive drugs in the long-term treatment of chronic alcoholics. Ann NY Acad Sci 252:385–395, 1988