

Letters From Scientists

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September 2, 2011

Nancy K. Stade
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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Re: **Docket No. FDA-2011-N-0504 – Please post for public viewing**

I trained research fellows at the National Institutes of Health (NIH) for 10 years. Thus, I am qualified to critique the FDA's recent review on CES. I have provided information about the NIH Intramural Research Program I coordinated as well as full disclosure information at the end of this letter (See page 5).

The purpose of my letter is to bring to your attention the very flawed FDA review on the effectiveness and safety of CES (Federal Register, Vol. 76, No. 172, Monday, August 8, 2011). I am appalled that the FDA would: (1) write and publish such an incomplete and inaccurate literature review, (2) specifically exclude relevant research studies on CES with significant outcomes from the review and (3) fail to include information on significant positive results of studies related to CES that were included in the FDA review. All of these FDA actions resulted in negative, inaccurate conclusions related to the safety and effectiveness of CES.

There are three major problems with the FDA review on CES:

- Incomplete and inaccurate FDA Summary of Data about effectiveness and safety of cranial electrotherapy stimulation.
- Illogical approach to anxiety studies using CES and inappropriate exclusion of studies from the review.
- No data to support four of the risks listed in the "Sec. 3 Risks" category.

Incomplete and inaccurate FDA Summary of Data about effectiveness and safety of cranial electrotherapy stimulation.

Instead of considering the literature on CES as a whole as the FDA is obligated to do, only a few studies out of the many available were included in the review. A decision related to the effectiveness and safety of a device should be made based on:

“...whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its condition of use (21 CFR Ch, 1 (4-1-07 Edition), page 175).”

Furthermore, the FDA specifically excluded the significant positive findings of some of the relevant research studies on CES because they lacked “a control.” According to the FDA, their Summary of the Data should be based on the following evidence:

Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts and reports of significant human experiences with a marketed device ... (21 CFR Ch, 1 (4-1-07 Edition), page 175).

The FDA’s own rule clearly indicates that valid scientific evidence includes “studies and objective evidence without matched controls.”

Below are some examples of your inaccurate review on CES:

- The FDA review states, the “Overcash study...used a rating scale that was not validated.” If the FDA had read the study (American Journal of Electromedicine), they would have found that the Overcash study used psychophysiological measures of anxiety – cardiovascular response (temp), glandular responses (EDR), and electromyography (EMG). All of these are accepted and validated approaches to measuring anxiety. A Numerical Visual Analog Scale (NVAS) was used to obtain a subjective measure of anxiety from the subject. Validity for the NVAS in the study of anxiety is well established in the research literature. The FDA comment on the rating scale used in the Overcash study is false.
- The FDA review states, “The Winick study...utilized a 7 point Likert scale, suffers from the same limitations” [did not use a standardized, validated rating scale]. The significant results that support the efficacy of CES and information on safety in the

Winick study were not included in the FDA review. The study, a RCT, actually used a visual analog scale (VAS) to measure anxiety. The VAS is the most commonly used scale in treatment outcome research and has established validity for the measurement of anxiety. The 7 point Likert Scale developed by investigators was used as a second measure of anxiety and its findings were consistent with the findings from the VAS scale. Thus, the Winick study also provides support for the validity of the Likert scale to measure anxiety. The FDA appeared to approach the review of CES through the lens of quantitative research only and the FDA reviewer does not appear knowledgeable about appropriate research measures for subjective feelings such as anxiety.

- The FDA inaccurately concludes that there is no evidence to support the safety of CES. The safety of CES is clearly established in the research literature. Further support for the safety of CES is included in a 2010 Cochrane review of *Non-invasive brain stimulation techniques for chronic pain* which included 8 CES studies. The Cochrane review states, “Non-invasive brain stimulation appears to be associated with minor and transient side effects (The Cochrane Library, ISSN 1464-780X).”

Currently, there are six on-going federally funded research studies on CES (see clinicaltrials.gov). Three are funded by the Department of Defense, two are funded by the National Institutes of Health, and one is funded by the Veterans Administration Medical Center. As evidenced by the federal government awarding funding for these studies, these studies obviously met the criteria for the effectiveness and safety of CES based on the research literature supporting the proposed studies.

Since 2009, eight new research studies, all with significant positive findings, that support the safety and effectiveness of CES have been completed, three were funded by the Veterans Administration Medical Center, one study each was funded by each of the following agencies: Office of Juvenile Justice and Delinquency Prevention (Federal Government), University of California at Los Angeles, Washington University at St. Louis and University of Virginia. One study, a double-blinded, placebo-controlled investigation doctoral dissertation was unfunded.

The Office of the Army Surgeon General in its May 2010 Final Report of the Pain Management Task Force provides support for the effectiveness and safety of CES. After a review of the scientific evidence, cranial electrotherapy stimulation was listed as a Tier II modality in the May 2010 report.

Illogical approach to anxiety studies using CES and inappropriate exclusion of studies from FDA review.

CES is cleared by the FDA for treatment of “anxiety” without any specific designation of type of anxiety. Your decision to limit the types of populations and type of anxiety included in your review – for example, “may not be indicative of an Axis I Anxiety Disorder” and to exclude CES studies of anxiety in people with “very specific” medical conditions is not logical. CES devices are prescription medical device and as such would be more likely to be used by individuals with medical conditions rather than the general population. An authoritative source, the DSM-IV-TR, provides a category of anxiety for those individuals with medical conditions. This classification approach is appropriate for these studies and could have been used in the FDA review (293.84 Anxiety disorder due to a general medical condition), rather than arbitrarily eliminating all CES studies with subjects who had specific medical conditions. Each of the individual studies that was excluded from the FDA review used a homogenous population. The consistent, significant positive outcomes of these studies that included diverse populations, when taken as a group provides strong and compelling evidence for the support of the safety and efficacy of CES. It is critical that these studies be included in a review to provide an accurate picture of the positive outcomes of CES.

There are no data in the literature to support four of the risks in Section C, “Risks”.

Only two of the six risks listed - headaches and skin irritation - should be listed as risks and these are mild and self-limiting. A headache usually goes away when the intensity of the current is decreased. Skin irritation can be decreased by moving electrode patches to different areas of the skin each time used. There is no support in the literature for the other four risks listed for CES. Two of these four risks are stated as fact which is blatantly wrong. There are absolutely no data to support these two statements.

Use of CES in my Practice.

I have used Alpha-Stim CES with patients who have anxiety, depression, and insomnia for over 15 years. It was both effective and safe. Nine out of 10 patients experience positive results after using Alpha-Stim CES; decreased anxiety, insomnia and/or depression. There have been no significant side effects with CES as compared to the often serious side-effects of medications used for these conditions. I have seen miserable individuals suffering from anxiety, depression and insomnia who are barely able to cope become peaceful and productive members of society with continued use of CES. I have had hospice patients who were suffering from severe anxiety, panic attacks and depression become calm and more alert when using Alpha-Stim

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CES. This made their last days more bearable for themselves and their families. As a practitioner using CES, it is not unusual to hear “Alpha-Stim [CES] changed my life!” from patients who have tried CES as a last resort when nothing else worked.

Summary.

Is there a need for larger and more rigorously controlled studies on CES? Definitely yes, research is an on-going process. Is there research support for the effectiveness and safety of CES? Absolutely, from a variety of valid sources. CES does not meet the criteria for a Class III device and there is ample support in the literature on the safety and effectiveness of CES to down classify it as a Class II device. **The FDA review on CES reflects poorly on the FDA's competency as a federal oversight agency, its knowledge and understanding about the research process and its ability to follow its own rules and regulations for the FDA review process.**

The FDA has published misleading and false information on CES to health care providers and the public. It is only fair, and reasonable, that the FDA conduct and publish a corrected, comprehensive review of CES.

Thank you for your prompt attention to this matter. You can contact me via phone, 202-255-6922, or e-mail at info@mchmedical.com.

Sincerely,

Francine Nichols

Francine Nichols, RN, PhD

Disclosure Information

As a full professor at the School of Nursing, Georgetown University, I was awarded the contract to conduct a research training program in molecular genetics for research fellows at the National Institutes of Health (NIH). I coordinated this program for the NIH for 10 years, from 2000 through 2009. The program accepted 20 – 22 NIH research fellows each year based on a highly competitive admission process. Scientists from the National Human Genome Research Institute and other Institutes at the NIH served as faculty for the program. A geneticist and I served as primary faculty for research proposal development in the program. Within one year after completing the program, over one-third of our NIH fellows received federal funding for the proposals they developed in the program.

Consistent with full disclosure, after I retired from NIH in October 2009 and returned to practice, I became an Alpha-Stim distributor. This enabled me to make CES more easily available through my practice to individuals who would benefit from using it.

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Personally, I have had “significant human experiences” with CES. I have used Alpha-Stim since 1996 after a serious shoulder injury and shoulder reconstruction surgery that left me with very limited range of motion of my left arm as well as CRPS and severe pain. When nothing helped, I searched the web for something that could help with the pain. I found Alpha-Stim, reviewed the literature and decided to try it. By the end of three years, I was off narcotics for pain and had obtained full range of motion of my arm. I attribute that to using Alpha-Stim microcurrent electrotherapy stimulation (MET) via electrode pads which decreased pain and to using CES which also decreased my pain level and increased my sense of well-being. CES and MET enabled me to complete a rigorous physical therapy program which I had been unable to do before because of the pain.

cc: Dr. Margaret Hamburg, FDA Commissioner
Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health
William Maisel, MD, MPH, Deputy Center Director for Science and CDRH Chief Scientist
Senator Daniel K. Akaka, US Senator for Hawaii
Senator Daniel Inyoue, US Senator for Hawaii
Representative Mazie Hirono, US Representative for Hawaii, Second Congressional District

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September 18, 2011

Nancy K. Stade
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Food and Drug Administration
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Re: The Federal Register, Vol. 76, No. 152, pgs. 48062-48070. Proposed Rule: "Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator." [Docket No. FDA-2011-N-0504].

Dear Ms. Stade:

In response to the request of the Food and Drug Administration (FDA) cited in the *Federal Register* on August 8, 2011 (76 F.R. 152, p. 48062) regarding its Proposed Rule for Cranial Electrotherapy Stimulation (CES), I am writing to inform you of my own findings regarding the safety and efficacy of CES.

In 1973, I founded and served as Executive Director of the UCLA Pain Control Unit and as a professor in the UCLA Medical and Dental Schools. Since that time, my colleagues and I have been involved in a variety of clinical research studies to explore the safety and efficacy of many unusual pain remedies, including acupuncture, herbal therapies, homeopathy, neurofeedback, and CES using the Alpha-Stim device.

Our studies concerning CES have focused on three major areas: pain control, addiction, and mood disorders (primarily anxiety and depression).

It is obvious that the Alpha-Stim is a rapidly effective and powerful pain control device. Just ask any patient in pain who has used it for even a minute or two. We have found it to be particularly helpful in treating patients with severe chronic pain, including those with Complex Regional Pain Syndrome (CRPS), trigeminal neuralgia, cluster headache (Horton's Cephalgia), peripheral neuropathy, and other neuropathic pain syndromes.

Without the Alpha-Stim, most of these patients require such high levels of pain medications that normal functioning is impossible and many remain restricted to bed. Using the Alpha-Stim, most of these patients require only minimal amounts of pain medications, and as a result, they are able to lead active and highly functional lives.

Because the Alpha-Stim releases beta-endorphins, we have used it extensively to treat a wide variety of addictions, including opiate dependence, cigarette and marijuana

smoking, and morbid obesity (usually caused by food addiction). We have found that the Alpha-Stim not only minimizes withdrawal symptoms as these patients are detoxified, but for most, it also obliterates urges and cravings when properly used. It has now become a mandatory component in all of our addiction treatment programs.

Members of our research team have been developing and testing smoking cessation programs for decades, and several years ago, one protocol that we developed was independently studied by researchers at Harvard Medical School in a three year study. They found that when compared to a control group, nearly 50% of the patients using our protocol were nicotine free one year later (as measured objectively by salivary cotinine swabs).

Although these findings are significantly more positive than any other smoking cessation protocol, we continued to study the subjects who were NOT successful, and found that in most cases, it was uncontrollable urges and cravings that sabotaged their success. By using the Alpha-Stim to suppress these cravings, we are now achieving over 90% success in our current smoking cessation studies. These findings are comparable to those of William Eidelman, MD, who has seen similar results.

There are currently over 60 million smokers in America comprising one of the largest populations of patients who will get catastrophic illnesses that could be prevented by an effective smoking cessation program. Thus, in addition to the health benefits that CES can provide to help smokers quit permanently, the positive economic impact this could have on health care costs is enormous.

While there are numerous studies documenting the effectiveness of CES in treating depression, we have also found it to be highly beneficial in treating a variety of anxiety disorders, including GADs, phobias, OCDs, performance anxiety, and PTSD.

During the years that I served as a White House Commissioner on Complementary and Alternative Medicine Policy, our commission heard testimony from scientists reporting many other positive findings regarding the safety and effectiveness of CES.

In terms of safety, the Alpha-Stim must rank as one of the safest therapeutic modalities known for effectively treating pain, addictions, and mood disorders. After using this device for over thirty years in a wide a variety of clinical situations, I can report that we have never seen any significant untoward effects, complications, or contra-indications. A few patients have reported mild skin irritation with prolonged use (such as following surgery). This has been easily and completely treated by employing a different location for the electrodes while the original site heals.

We have used the Alpha-Stim on many occasions to relieve migraine headaches, and have never heard a patient report that it caused one. Likewise, we have recommended CES to epileptic patients with chronic pain, and have never heard of it triggering a seizure.

It is very gratifying to give patients in pain an effective therapeutic modality like the Alpha-Stim, knowing that they can't hurt themselves with it no matter what they do.

The same cannot be said when we give them a prescription for pain medicine or recommend interventional procedures such as epidural stimulators or opiate infusion pumps.

It would be catastrophic if CES devices such as the Alpha-Stim become even more restricted at a time when it is needed by American citizens more than ever. It is my hope that FDA will allow CES to be down-classified to a Class II device as it is clearly and obviously both safe and effective given the reports of reputable investigators who have been using it extensively for decades..

Thank you for your attention to this matter

Sincerely yours,

David E. Bresler, PhD, LAc, DiplAc(NCCAOM), DiplAAPM
Founder and Former Executive Director of the UCLA Pain
Control Unit, and Associate Clinical Professor of Anesthesiology,
Gnathology and Occlusion, and Psychology, UCLA Schools of
Medicine and Dentistry, and the UCLA College of Letters and Sciences
White House Advisor

DEB:mmc

November 5, 2011

Nancy K. Stade
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Food and Drug Administration
5630 Fisher Lane, Room 1061
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Re: The Federal Register, Vol. 76, No. 152, pgs. 48062-48070. Proposed Rule: “Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator.” [Docket No. FDA-2011-N-0504].

Dear Ms. Stade:

I am submitting this response at the request of the Food and Drug Administration (FDA) in its Proposed Rule for Cranial Electrotherapy Stimulation (CES) issued in the *Federal Register* on August 8, 2011 (76 F.R. 152, p. 48062). As a statistician who is actively involved in CES research, I want to share with FDA my own findings on the efficacy and safety of CES. However, before sharing my opinion and insights regarding the efficacy and safety of CES, I acknowledge that I serve as Director of Research for Electro Medical Products International (EPI) on a part-time basis. My role and responsibilities as Director of Research for EPI is to consult with independent researchers to ensure the veracity and rigor of their research design and statistical analyses related to CES studies. My primary occupation is Director of Faculty Research and Professor of Psychometrics and Statistics at Texas State University in San Marcos Texas. As Director of Faculty Research, I work collaboratively with scholars and researchers in the Colleges of Science, Computer Science, Engineering and Liberal Arts to (a) conceptualize and write competitive grant proposals for submission to the National Science Foundation, National Institutes of Health, Institute of Education Sciences, National Institutes of Mental Health, and (b) ensure the research design and analytic strategies are innovative, sound and rigorous for their research. I serve as an objective reviewer for numerous top-tier peer reviewed journals in quantitative methodology and certainly take pride in the objective nature of my professional reviews, however, given my role as Director of Research at EPI, I acknowledge that my recusal is warranted as related to being viewed as an impartial evaluator of CES research using Alpha Stim technology. In the following paragraphs, I briefly review six studies conducted independent of United States Government funding mechanisms that were conducted with a high level of rigor and therefore provide objective results. Specifically, the following studies support the efficacy and safety of CES therapy as delivered using Alpha Stim technology on anxiety, pain, depression and insomnia.

In a rigorous randomized controlled double-blind trial (RCT) on **anxiety** conducted by Winick, (1999) titled: Cranial electrotherapy stimulation (CES): a safe and effective low cost

means of anxiety control in a dental practice, *General Dentistry*, 47(1):50-55. In the study, the author uses the Visual Analog Scale (VAS), a well-established instrument with established evidence of validity and reliability for measuring change in anxiety from baseline to posttest. The sample size for the active CES group was N=16 and for the placebo group, N=17. The findings are corroborated using a separate instrument (i.e. Likert scale measuring degree of change) measuring perceived anxiety. The author reports confidence intervals based on the standard error of measurement, a particular strength because the SEM accounts for the reliability of the instrument in conjunction with any mean differences between treatment groups. The author concluded that using CES during various dental procedures significantly comforts dental patients, who experience extreme levels of anxiety. Many members of the treatment group requested CES at subsequent visits, and none objected to it. The low cost, safety and ease of use of CES recommends its freer trial to enhance patient comfort during various routine dental procedures. There were no detectable adverse effects.

Voris (1995) conducted a triple blind randomized study on **anxiety** titled: An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among outpatient psychiatric patients, impulse control parolees and pedophiles, published by the Delos Mind/Body Institute, Dallas and Corpus Christi, Texas. The author uses the State Trait Anxiety Inventory (STAI), a valid and reliable instrument that I have professional experience with while working as a Psychometrician at The Psychological Corporation between 1999 and 2001. Additionally, the author uses two physiological measures (EMG and peripheral skin temperature) to triangulate his findings. Subjects exposed to CES exhibited significant improvement from baseline to posttest ($p < .001$). Importantly, the author stated that when they began the research, several members of the team had significant doubts as to the effectiveness of this technology. In addition, the concerns of FDA caused further concern and suspicion regarding this technology. But after this project, they concluded that they are completely convinced as to the value of this treatment methodology for many of their patients. No adverse side effects were reported.

Cork, et al. (2004), conducted a double blind randomized study titled "The effect of cranial electrotherapy stimulation (CES) on **pain** associated with fibromyalgia" *The Internet Journal of Anesthesiology*, 8(2). The Alpha-Stim treatment group (N=39) had significantly lower scores after a 3-week period than the sham group (N=35) on the Profile of Mood States (POMS), Oswestry Scale, McGill Pain Instrument, and Tenderpoint Pain Assessment instruments indicating less depression ($p \leq .01$). The instruments used in his study are reliable and valid for the purpose of this research. The findings revealed that CES can play a significant role in the treatment of pain associated with fibromyalgia. The authors concluded that CES appears to be an effective, well-tolerated treatment for fibromyalgia. Those involved in the treatment of fibromyalgia should include it in their clinical armamentarium, given the demonstrated safety of this noninvasive modality.

Lichtbroun, et al. (2001) published the results of his investigation titled: The treatment of fibromyalgia with cranial electrotherapy stimulation in the *Journal of Clinical Rheumatology*. 7(2):72-78. The study included a double-blind, placebo-controlled design in which 60 randomly assigned patients over a 3 week period were exposed to CES, sham, or placebo. Treated patients

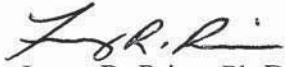
demonstrated a significant improvement in tender point scores ($p < .01$), and a significant improvement in self-rated scores of general pain level ($p < .002$). The number of subjects rating their quality of sleep as poor dropped from 60% at the beginning of the study to 5% ($p < .02$). In addition, there were significant gains in the self-rated feeling of well-being ($p < .05$), and quality-of-life ($p < .03$), plus fairly dramatic gains in 6 stress related psychological test measures of the Profile of Mood States. No placebo effect was found among the sham treated patients. The Alpha-Stim treatment group had less **anxiety** compared to the sham group ($p = 0.05$). The Alpha-Stim treatment group also had less **depression** from pre-test to post-test. Additionally, quality of **sleep** significantly improved ($p < .001$) as did overall **well-being** ($p < .001$) and self-rated **pain**.

Mellen, et al. (2009) conducted an investigation titled “Reducing sheriff’s officers’ symptoms of **depression** using cranial electrotherapy stimulation (CES): a control experimental study. *The Correctional Psychologist*, 41(1):9-15. In this study, 21 volunteer officers from a sheriff’s staff, 10 males and 11 females were randomly assigned to either the treatment ($N = 10$) or control (sham treatment, $N = 11$) groups and were blind to group assignments. All subjects completed 20, 20 minute sessions of CES exposure. Dependent measures used included the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the Brief Symptom Inventory (BSI) which has both depression and anxiety scales – instruments that I have personally worked on as a Psychometrician at The Psychological Corporation and can attest to their exceptional level of psychometric quality. Significant improvements on the BSI Depression scale ($P < .01$) and the BDI ($P < .05$) scores were found. The BAI did not reveal significant results, however a Sign test (trend analysis) revealed 10 of the remaining 11 BSI subscales indicated significant downward directions of difference ($P < .01$) in the treatment group when compared to the control group. These findings suggest a broad trend towards reduction in the full range of clinical symptoms and may support the theory that the Alpha-Stim CES has a global modulating effect on brain dysfunctions.

A final study recently completed at the University of Virginia with a publication in progress for 2012 is by Taylor, et al. titled: Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia. This study includes the most rigorous RCT methodology and analytic approach to investigate the effect of CES on pain and insomnia I have reviewed to date. The Taylor et al. study included 46 subjects in the sham or placebo group and 17 in the active CES group. The study is particularly strong because in addition to it being a true double-blind protocol, the study period included an 8 week, daily exposure treatment period and uses a random effects mixed model for analyses as opposed to analyses based on the traditional fixed-effects general linear model. Results indicate that the active CES group exhibited less pain and insomnia compared to sham group ($p < 0.001$).

Thank you for your attention to this matter. It is my hope that FDA will allow CES to be down-classified to a Class II device as it has proven itself to be both safe and effective. Please feel free to contact me should you have further questions.

Sincerely,



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