

SPONSOR: Fisher Wallace Laboratories, LLC

PANEL: Neurological Devices Panel

DATE: February 10, 2012

Reclassification of Cranial Electrotherapy Stimulation (CES)

SPEAKERS

Charles Avery Fisher

Richard P. Chiacchierini, Ph.D.

Mitchell Rosenthal, MD

Brigadier General (Ret.) Stephen N. Xenakis, MD

CES as a Device Type

- Maximum current: 4 mA
- Alternating Current
- Battery Power Source
- Using rTMS Guidance Documents as a Model

Current Indication (Class 3)

Cranial Electrotherapy Stimulation is indicated for the treatment of depression, anxiety and insomnia.

Indication for Class 2

Cranial Electrotherapy Stimulation is indicated for the treatment of depression, anxiety and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication.

DEVICE CLASSIFICATION

Class 1 – Simple Design, Low Risk

Class 2 – More Complex, Higher Risk

Class 3 – Most Complex, Highest Risk

Class 3 is typically reserved for devices that:

- Support / Sustain Human Life
 - CES DOES NOT
- Have a potential unreasonable risk of illness or injury
 - CES DOES NOT

Class 2 (in 2011)

Transcranial Magnetic Stimulation (TMS)

Non-Invasive / Non-Surgical

Indicated for patients who have failed on drug therapy

10 – 100X Greater current strength than CES

Guidance Documents for rTMS a model for
Reclassifying CES

Proposed Class 2

Cranial Electrotherapy Stimulation

Non-Surgical / Non-Invasive

Very Low Amperage (0-4 mA)

No Serious Side Effects

40+ Years on the Market

Well Controlled Investigations on a subset of the population

Outstanding clinical impressions from world-class psychiatrists

Psychiatrists Who Endorse Class 2 Status

- Chief of Psychiatry at Mass General Hospital
- Chairman of Psychiatry at NYU Medical School
- Many more + hundreds prescribe



MASSACHUSETTS
GENERAL HOSPITAL



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Jerrold F. Rosenbaum, MD
*Psychiatrist-in-Chief
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*Stanley Cobb Professor of Psychiatry
Harvard Medical School*

Jan. 5, 2012

Ms. Christy Foreman
Director, Office of Device Evaluation
Food and Drug Administrative Center for Devices and Radiological Health
Document Mail Center-W066-G6091093
New Hampshire Avenue
Silver Spring, MD 2093-0002

Dear Ms. Foreman:

I am a clinician and clinical researcher with a substantial background in mood disorders research and clinical innovation, Chief of Psychiatry at MGH and a Professor of Psychiatry at HMS. I am writing to support reclassification of Cranial Electrotherapy Stimulation (CES) as a Class 2 medical device; I have not been compensated by any CES manufacturer nor have a financial interest in CES in any way, but am writing simply as one who specializes in difficult to treat mood disorders and has at times engaged alternative options in my effort to help those who suffer. Along the way, in weighing risks and benefits, I have encouraged some patients to use this device and have seen benefit.

I support CES receiving Class 2 status in light of its safety in fairly extensive use and positive results observed by many who use it. This appears to be a very low risk device without serious side effects. Colleagues of mine have initiated a controlled trial and I am eager for those results with respect to efficacy. With adequate labeling and manufacturing standards, CES can be a safe and alternative option for patients, especially those who have done poorly or inadequately or have not tolerated drugs. I would also point out the device's affordability compared to the cost of other brain stimulating device based psychiatric treatment such as rTMS or ECT.

If it would be of help to answer any questions, please feel free to contact me.

Sincerely,

Jerrold F. Rosenbaum, MD

THE US ARMY HAS OFFICIALLY REQUESTED EXPEDITED REVIEW OF CES RECLASSIFICATION

- CES is currently used in Army, Navy and VA Hospitals
- Enormous Target Population
- Many Drug Resistant Patients
- Substance Abuse Common



DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

Food and Drug Administration

January 13, 2012

Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Attn: Ms. Christy Foreman
Director, Office of Device Evaluation, CDRH, FDA

Re: Request for Expedited Review of Reclassification for Cranial Electrotherapy Stimulation devices, FDA-2011-N-0504

On behalf of the U.S. Army, I am writing to respectfully request that the Food and Drug Administration ("FDA") perform an Expedited Review of the reclassification petition regarding Cranial Electrotherapy Stimulation devices. The petition proposes reclassifying Cranial Electrotherapy Stimulation ("CES") devices as Class 2 medical devices. The commercial availability of CES devices offers a potential treatment option for soldiers and veterans who suffer from neuropsychiatric conditions commonly seen on redeployment from combat duty. Subjecting CES manufacturers to the burdensome PMA process may bankrupt these companies and permanently disrupt the availability of CES devices.

CES devices are eligible for expedited review for the following reasons:

1. Cranial Electrotherapy Stimulation devices are proposed to treat serious (in the case of suicidal patients) or irreversibly debilitating psychiatric conditions in patients suffering from depression, anxiety and insomnia, often in association with Post Traumatic Stress and substance abuse.
2. CES devices have been prescribed for the treatment of soldiers and veterans with neuropsychiatric conditions who do not respond to psychotropic medications or do not comply with prescriptions. The Veterans Affairs study published in JAMA entitled "Adjunctive Risperidone Treatment for Antidepressant-Resistant Symptoms of Chronic Military Service-Related PTSD: A Randomized Trial" documents the limited efficacy of drugs in the treatment of depression in soldiers who are suffering from PTSD.
3. The continued and uninterrupted availability of these devices for further study is in the best interest of patients.

Thank you for your consideration. I have faxed a copy of this letter to the Director of the Office of Device Evaluation's Program Operation Staff, Mr. Robert Gatling. Please feel free to contact me if I can provide any additional information: 301-619-7591, dallas.hack@us.army.mil.

Sincerely,

A handwritten signature in black ink that reads "Dallas C. Hack MD".

COL Dallas C. Hack MD
Director, Combat Casualty Care Research Program
US Army Medical Research and Materiel Command

Special Controls

A combination of General Controls and Special Controls will provide a reasonable assurance of safety and effectiveness.

Statistical Review of Effectiveness and Safety for CES

Richard P. Chiacchierini, Ph.D.
President, R. P. Chiacchierini &
Associates

Effectiveness Studies

- All studies are small (10-64 subjects total), in different populations (drug/alcohol withdrawal, psychiatric disorders, and insomniacs), and with different CES exposures
 - Difficult populations to study sometimes with high non-compliance or drop-out rates
- Reviewed Studies
 - Six randomized studies in humans and one animal study support effectiveness (1973-1998)
 - Two randomized studies fail to show effectiveness (1974 and 1992)
 - Three non-randomized studies show biomarker changes
- Unlike in negative studies, in positive studies, small sample size does not have power consequences but comparability and adjustment techniques have limited capabilities
- Statistical analyses not always complete but appear to be representative of journal and year of publication

Effectiveness Support (Human) 1

- Randomized (1:1) double-blind study of 10 confirmed insomniacs with no underlying psychopathology in a sleep laboratory evaluation
- Baseline characteristics appear to be balanced but tests are likely underpowered
- Twenty-four 15 min daily treatments demonstrated reduced sleep onset latency and time in bed awake in CES cases but not in the Sham cases by blinded, objective EEG evaluations; results correlated with subjective questionnaires asking impressions of latency and wakefulness during sleep; and no adverse events reported
- Benefits sustained after 2 weeks of no stimulation

Weiss, M., The treatment of insomnia through the use of electrosleep: an EEG study. *The J. of Nervous and Mental Disease* 157:108-120, 1973.

Weiss Results – Primary Variables in 10 Insomniacs

Variable	Treatment	N	Mean Pre	Mean Post	2wk Mean Follow-up
Sleep Onset Latency	CES	5	60.8	10.6	6.2
	Sham	5	60.5	58.8	35.9
P-Value			0.903	0.041	0.026
Total Bed Time Awake*	CES	5	19.334	4.192	2.448
	Sham	5	17.296	18.500	11.550
P-Value			0.680	0.012	0.023

*After Sleep Onset

Effectiveness Support (Human) 2

- Randomized (1:1) double-blind study of 20 habitual alcoholics with non-AWS affective disorders who were alcohol abstinent 3-4 weeks
- Balanced in baseline characteristics except age (CES group older 39.5 vs. 36.0) and no discussion of study completion rates
- 30 minute exposures daily for 4 weeks showed strong statistical significance in favor of CES group in Zung's test (depression), Reactive Anxiety test, MMPI (Taylor) Anxiety, MMPI (depression)
- MAO-B activity and GABA levels elevated from baseline in CES arm but not in control - difference between groups not statistically significant
- No change in serotonin, dopamine, or β -endorphin
- No report of adverse events

Krupitsky et al. The administration of transcranial electric treatment for affective disturbances therapy in alcoholic patients. *Drug and Alcohol Dependence* 27:1-6, 1991

Krupitsky et al. Results in 20 Alcohol Withdrawal Patients

Variable	Treatment	N	Baseline	Day 14	Day 29*
Zung's Test	CES	10	55.3	47	39.6
	Control	10	54.2	55.8	57.5
	P-Value		ns	<0.05	<0.01
Reactive Anxiety	CES	10	51.7	43.0	39.6
	Control	10	51.7	50.6	53.0
	P-Value		ns	ns	<0.05
MMPI (Taylor Anxiety Scale)	CES	10	26.6	18.0	14.0
	Control	10	28.5	26.8	28.0
	P-Value		ns	<0.05	<0.05

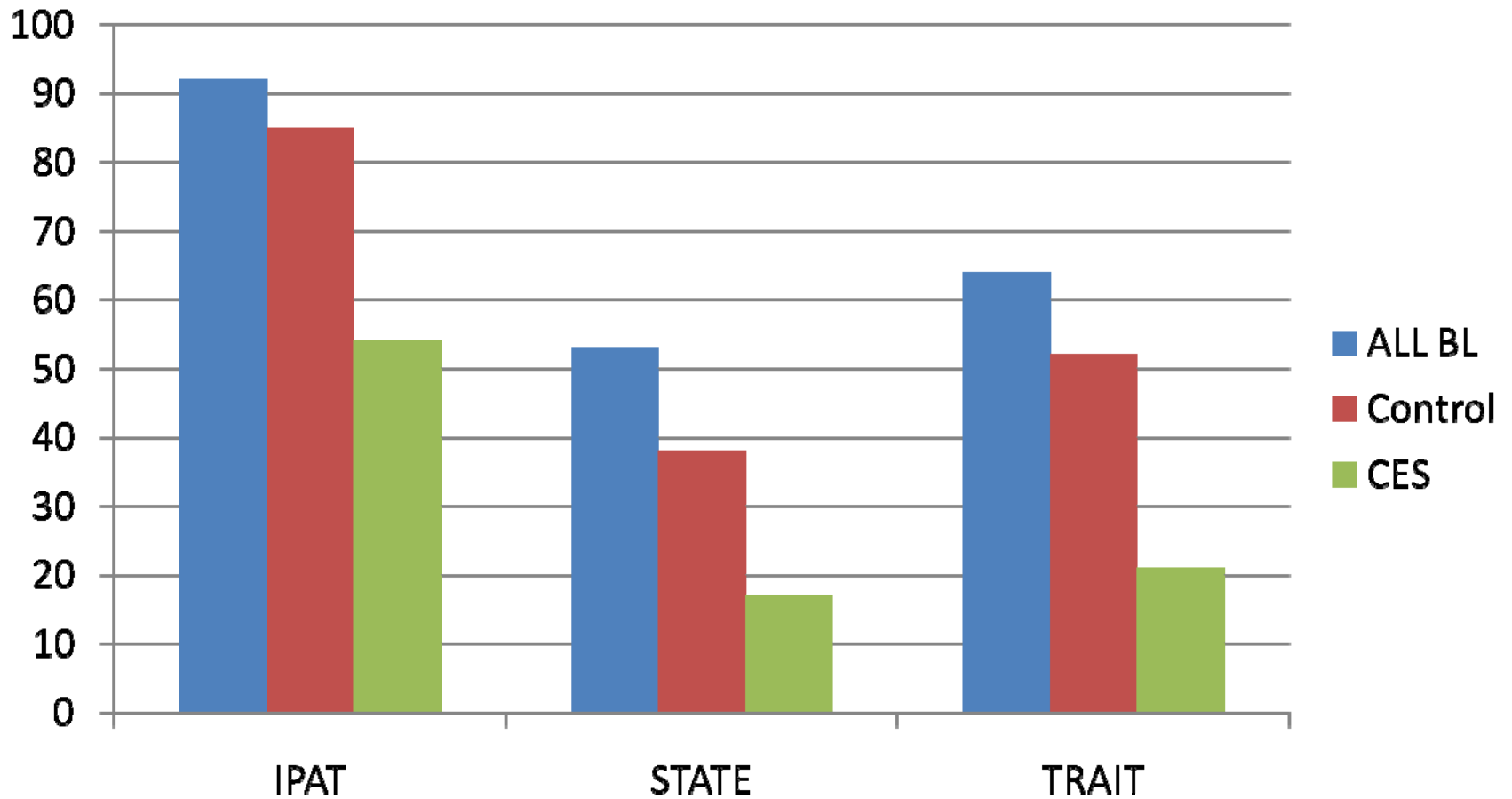
*One day after last of 20 treatments

Effectiveness Support (Human) 3

- Randomized (3 CES:1 Sham) double-blind study of 40 inpatient alcohol or poly-drug users with anxiety (no psychotropic drugs allowed during study)
- No analysis of baseline characteristics and no discussion of study completion rates provided
- Fifteen 30 min sessions over 3 weeks showed strong reduction in State/Trait Anxiety Indices (3) and Profile and Mood States among CES but not Sham subjects
- No difference in response between older and younger subjects or between alcohol vs drug abusers
- No report of adverse events

Schmitt, R. and T. Capo. Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. *Alcoholism Cl. And Exp. Res.* 10:158-160, 1986

Schmitt et al. Anxiety Results in 40 Inpatient Chemically Dependent Patients

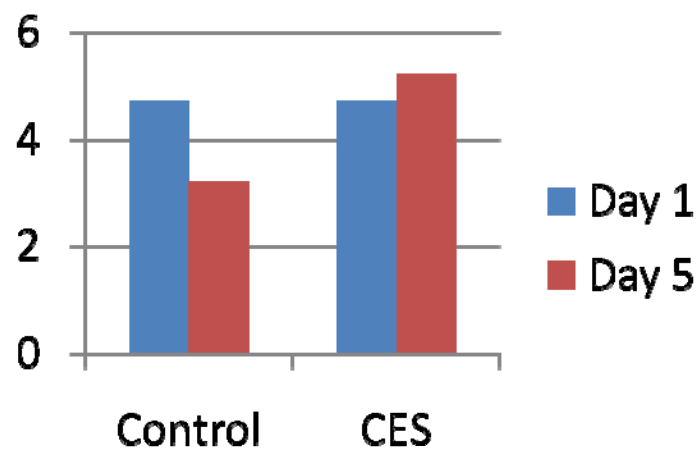
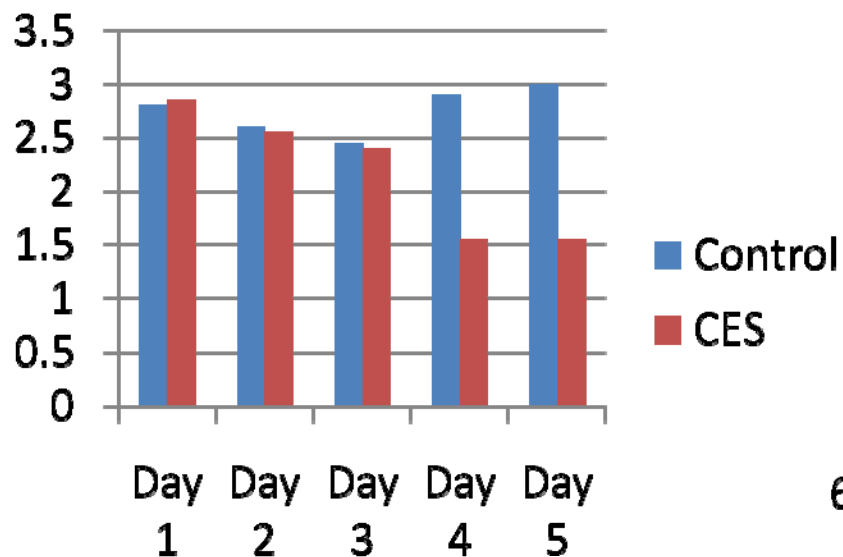


Effectiveness Support (Human) 4

- Randomized (1:1) double-blind study of 21 psychiatric inpatients suffering depressive disorders with no active drug treatment during stimulation
- Baseline characteristics not significantly different, but point estimates are not close for some variables (age, gender, length of illness)
- Two 30 min treatments over 5 days showed significant declines in anxiety and increases in awakening time in CES patients but not in controls during the 5-day withdrawal period (from treatment drugs); and no report of adverse events
- No direct comparison of differences from baseline were done or could be done from the data presented

Philip et al. 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

Philip et al Anxiety and Hrs of Sleep Results in Drug Withdrawal



Effectiveness Support (Human) 5

- Randomized study of 28 former heroin addicts undergoing treatment for methadone withdrawal (14 CET, 7 sham and 7 non-sham controls)
- Balance of baseline characteristics not tested, but anxiety scores in same range for all three groups
- Ten 30 min sessions over 14 days demonstrated significantly reduced anxiety levels (Taylor) and dramatically reduced methadone intake in the 13 CET subjects remaining in the study but no change in either control group for anxiety levels
- Some of the reductions above not supported by P-values
- No report of adverse events

Gomez, E. and A. Mikhail. Treatment of methadone withdrawal with cerebral eletrotherapy (electrosleep). *Brit. J. Psychariat.* 134:111-113.

Gomez and Mikhail Anxiety Results in Drug Withdrawal

Variable	Treatment	N	Baseline	Day 10
TMAS (Anxiety) Normal	CES	14	0/14	7/14
	Control	14	0/14	0/14
	P-value		ns	0.006
Continued Methadone Use	CES	14	14/14	5/14
	Control	14	14/14	14/14
	P-value		ns	0.0006

Lack of Effectiveness (Human) 1

- Randomized double-blind study of 28 psychiatric outpatients on reduction in symptomatic days and symptom sensitivity
- Baseline characteristics were not tested and some appear to be different (age and primary psychiatric diagnosis)
- Five daily 30 min treatments showed no statistically significant difference in symptom-free days of on day 5 and 19 after initial treatment . A second variable recording whether symptoms bothered subject was significant in favor of CES on day 5, but not on day 19
- Relevance of endpoints especially long after cessation of treatment is questionable
- No report of adverse events

Lack of Effectiveness (Human) 2

- Randomized double-blind study of 25 cocaine and 18 opiate dependent male subjects during withdrawal
- No analysis of baseline characteristics and patients appear to be on methadone during the trial
- Continuous exposure for 7-10 days failed to show statistically significant effect of CES on withdrawal scales, however all sham subjects received low level of current thought to be incapable of producing effect by authors in this study
- No reports of adverse events
- Authors admit that sham exposure could be therapeutic and that measurement questionnaires may be inadequate to detect changes in withdrawal symptoms in this population

Gariti et al. A randomized double-blind study of neuroelectric therapy in opiate and cocaine detoxification. *J. of Substance Abuse* 4: 299-308, 1992

Human Biological Marker Studies

- Three non-randomized studies:
 - Increased serotonin and decreased tryptophan after exposure to two active CES devices but not for control TENS device shown in 14 volunteers (Liss. S. and B. Liss. Physiological and therapeutic effects of high frequency electrical pulses. *Integrative physiological and behavioral science* 31:88-94, 1996)
 - Significant serotonin and beta endorphin changes in cerebral spinal fluid in 5 volunteers and beta endorphin, melatonin and norepinephrine in plasma shown in 10 volunteers (includes the 5 above) (Shealy et al. Cerebrospinal fluid and plasma neurochemicals: response to cranial electrical stimulation. *J. Neurol. Orthop. Med. Surg.* 18: 94-97, 1996)
 - Elevated serotonin levels shown in 11 severely depressed subjects but not 14 normal subjects or 23 chronic pain patients (Shealy et al. Depression: a diagnostic, neurochemical, profile & therapy with cranial electrical stimulation. *J. Neurol. Orthop. Med. Surg.* 10: 319-321, 1989)
 - No report of adverse events in any study.

Liss and Liss BioChemical Changes in Blood Plasma

Bio-Chemical	TENS Stimulation		Electric Stimulation Peripheral		Electric Stimulation Transcranial	
	Before	10 min After	Before	10 min After	Before	10 min After
Serotonin ng/ml	54.40	55.27	63.27	86.13	45.00	76.00
Tryptophan Rel (%)	50.13	49.47	55.40	45.20	51.10	37.20
Cortisol ng/ml	13.27	12.17	12.73	10.99	15.35	13.71
ACTH pg/ml	19.61	19.43	18.82	24.42	7.42	12.52
B –Endorphine pg/0.1ML	9.38	8.78	10.60	12.54	12.29	16.73

Shealy et al Biochemical Changes after CES in 11 Severely Depressed Patients

Biochemical	Mean (SD) Before Treatment	Mean (SD) After 2 Wks Treatment	P-value
Serotonin	33.15 (9.33)	44.64 (9.10)	0.0089
Cholineserase	13.82 (2.86)	10.45 (2.30)	0.0087

Summary

- Effectiveness
 - Admitting the limitations of the studies evaluated, human and animal randomized studies show clinically effective and statistically significant changes to some studied conditions in selected populations following electrical stimulation to the head, and
 - Human studies provide evidence that electrical stimulation of the head produces changes in biochemical components in blood and cerebral spinal fluid that may be associated with the clinical changes found in the randomized studies
- Safety - no reports of adverse events

CES in Clinical Practice: Substance Abuse Rehabilitation

Mitchell Rosenthal, MD
Founder, Phoenix House

Table 2. Comparison of attrition rates between clients who received CES and clients who did not receive CES.

	no CES	received CES
Residential treatment attrition	n = 293	n = 99
	n (%)	n (%)
at day 7	29 (9.9)	0 (0.0)
at day 14	62 (21.2)	3 (3.0)
at day 30	89 (30.4)	10 (10.1)
at day 60	120 (41.0)	17 (17.2)
at day 90 *	131 (48.3)	23 (24.0)

* *Note:* Sample sizes were n=271 and n=96 for the no-CES and CES groups respectively. Excluded from 90 day attrition analyses are 8 clients who completed residential treatment between 60 and 90 days, and 17 clients admitted at the end of May 2009 who have not reached the 90 day timepoint.

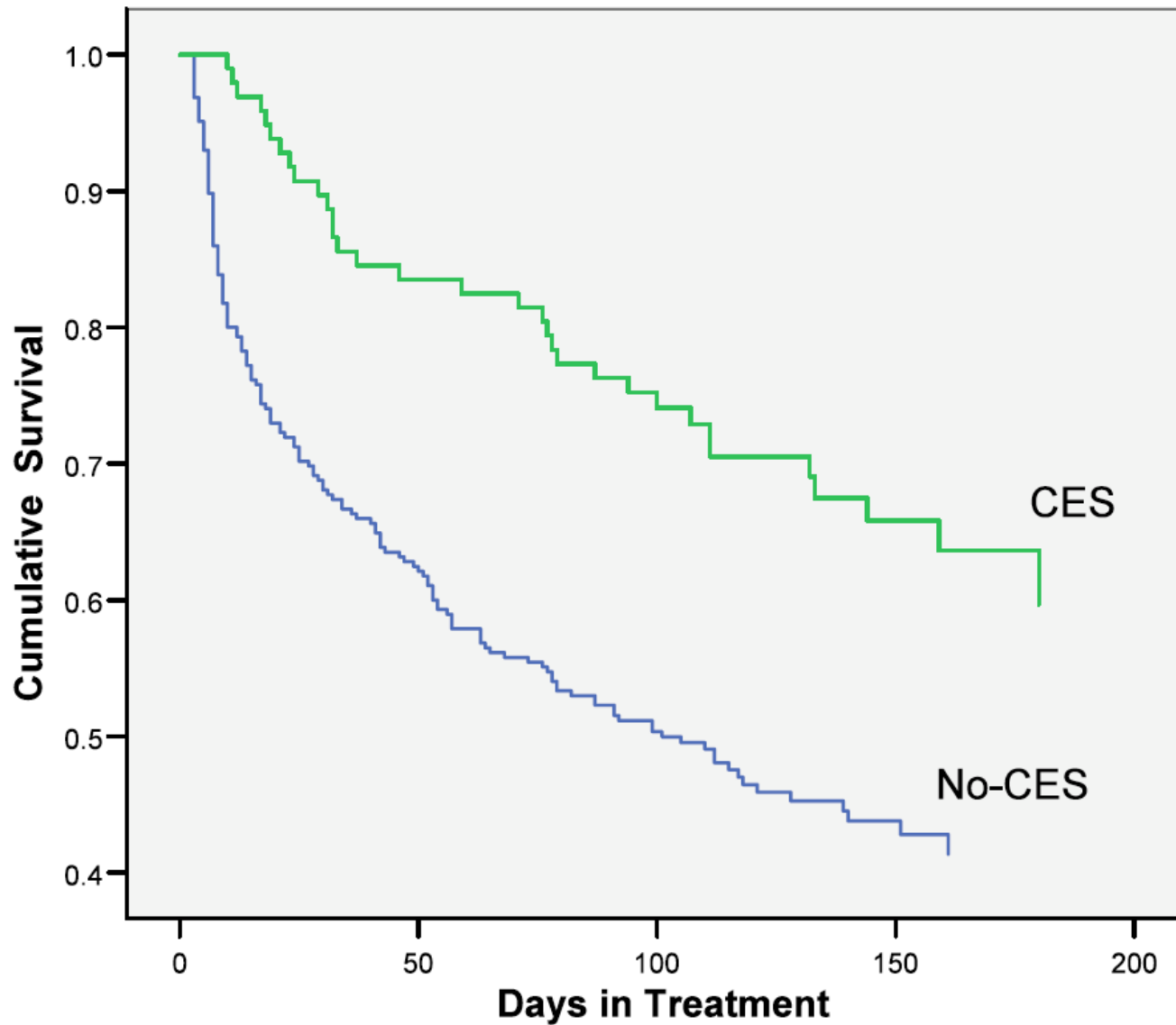


Fig. 1. *Cox regression model (unadjusted) showing treatment retention for clients who participated in CES and clients who did not*

CES in Clinical Practice: Military & Veterans

Stephen N. Xenakis, M.D.
Brigadier General (Ret)
U.S. Army

OIF/OEF: Scope & Challenges

- 2.5 M service members deployed
- 40% manifest complaints – 1.0 M
- Common – emotional, post-concussion, pain, sleep, pain, etc.
- Suicide in the Army –262 for FY2011
- Record shows - 1/3rd involving Rx
- Toxic mixing of Rx – 101 deaths from 2006-9

Post-Deployment: **Co-occurring Conditions**

- **Alcohol & substance abuse**
- IED blast concussions
- PTS & other emotional reactions
- Sleep disturbance
- Misconduct
- Musculoskeletal pain

Alcohol & Substance Abuse

- ***JAMA. 2008; 300 (6), 663-675***
- Prevalence
 - Heavy weekly drinking : 9-12 %
 - Binge drinking: 53 %
 - Alcohol related problems: 12-15 %
- Increased risk for Reserve & NG
- Increased in younger age groups

Combat & Mental Health

- *Arch Gen Psych. 2010; 67(6); 614-623.*
- PTSD or Depression
 - Serious impairment: 8.5-14 %
 - Some impairment: 23.2-31.1 %
- **Alcohol abuse & aggression: co-morbid in 50%**
- Increase over 3-12 months for Nat'l Guard
- Persistent effects of combat
- No data on mTBI

IED Blast Concussions: Signature Injury

- Symptoms: irritability, affective lability, fatigue, sleep disturbance, and impaired cognition
- ***Journal of Head Trauma Rehabilitation:***
January/February 2010: Vol 25 (1) 9-14: - 15%
- RAND: exposure to IEDs – 40 %
- ***Journal of Neurotrauma:*** “...quality of evidence did not support any treatment standards and few guidelines...”
- **IOM (2011):** evidence ... is variable ... insufficient ...to provide definitive guidance

Pain & Pain Relievers

- *Generating Health & Discipline in the Force:*
 - Most commonly misused drugs
 - Higher survival rate – more chronic pain (47% of returning soldiers)
 - 14% prescribed opioid
 - Leading cause of disability
 - Fatal poisonings tripled since 1999
- *Army Pain Management Task Force (2010)* – leverage alternative & complementary treatments

Gaps: Clinical Care & Research

- PTSD: some evidence for Intensive Exposure Therapy (IOM)
- Psychotropic medications
 - Not effective for 25% (*Arch Gen Psychiatry. 2011;68(12):1227-1237*)
 - <1/3 of depressed patients achieve remission in 8 weeks (STAR*D: *Am J Psychiatry 2007;164:201-204. 10.1176/appi.ajp.164.2.201*)
 - Noncompliance in SUD – 42% (*Am J Addict. 2005; 14(3): 195–207*)
- IED post-concussion – only CRT (IOM, 2011)
- Rx – over-prescribed for sleep & pain

DoD Initiatives for mTBI

- Clinical Practice Guidelines
 - – TBI clinical practice guidelines and clinical support tools profiles and analysis
 - – Cognitive Rehabilitation in TBI
 - – Management of Severe TBI treatment literature review
 - – Altitude effects on TBI literature review
 - – Sleep and TBI literature review
 - – Neuroendocrine sequelae of TBI literature review
 - – Toolkit for Treating mTBI and Co-Occurring Conditions
 - § Rehabilitation / Recovery / Reintegration
 - – DVBIC -Virtual TBI Clinic (VTC)
 - – National Intrepid Center of Excellence (NICOE)
 - § Dissemination to the field

Identifying Promising Treatments

- Criteria:
 - Safe & Reasonably Effective
 - Currently used
 - Practical
 - Economic
- Develop & Deploy

Low Risk

- Far below seizure threshold
- Electrical field – 100x less than ECT or TMS
- CES designed to match dynamic electrical impedance of the body
- Differs from ECT – designed to induce seizures
- No reported adverse events (seizures)
- Anti-anxiety effect & “reduced seizure risk”

Significant Evidence
of Effectiveness

+

Human Biological Marker Studies

Benefits outweigh Risks

- Helps insomnia, anxiety, depression, & pain
- Unique in alcohol & substance abuse
- Safe – non-pharmacologic
- Benefits symptoms common following combat
- Adjunctive with Rx & Alternative when Rx fails