From: Richard Abrams <richard.abrams@gmail.com>
Sent: Wednesday, July 1, 2009 4:59 AM
To: Krauthamer, Victor
Cc: Conrad Swartz
Subject: Re: Safety & Efficacy of ECT Device?
Attachments: EFFICACY_AND_SAFETY_OF_ECT_7-1-09.doc

Dear Dr. Krauthamer,

Attached is a WORD file of the most recent draft of Somatics' submission in response to the FDA order.

We look forward to your comments.

Regards,

Richard Abrams

On Tue, Jun 23, 2009 at 6:01 PM, Krauthamer, Victor <Victor.Krauthamer@fda.hhs.gov> wrote:

> Dear Dr. Abrams,
>
> I on vacation this week in Olympia, Washington. But we certainly want to help assist with the process and preview your firm's submission. I will be happy to look at what you plan to send. Please feel free to email it to me, but I probably will not be able to read until after July 1.
>
> Best regards,
>
> Victor Krauthamer, Ph.D.
> Scientist
> Office of Science and Engineering Labs
> Center for Devices and Radiological Health
>
> -----Original Message-----
> From: Richard Abrams [mailto:richard.abrams@gmail.com]
> Sent: Tue 6/23/2009 1:08 PM
> To: Krauthamer, Victor
> Cc: Conrad Swartz; Sarah H Lisanby
> Subject: Safety & Efficacy of ECT Device?
>
> Dear Dr. Krauthamer,
>
> I am a Director of Somatics LLC, manufacturer of the Thymatron ECT device. I'm writing at the suggestion of Dr. Holly Lisanby who said you might be interested in hearing from ECT device manufacturers who were responding to the recent FDA order for submission of safety and efficacy data.

We have essentially completed our submission, and I was wondering whether you would be willing to have a look at it before we send it in; if so, I could attach it as a WORD file to an email message.

I look forward to hearing from you.

Sincerely,

Richard Abrams, M.D.

Director
Somatics LLC

TO: Division of Dockets Management (HFA-305)
Food & Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

FROM: Somatics LLC
910 Sherwood Drive #23
Lake Bluff IL 60044

DATE: 7/1/2009

RE: Docket No. FDA-2009-M-0101
21CFR Regulation 882.5940
Establishment Registration Number 1420295
Premarket Submission Number K945120
Premarket Submission Number K955576

The following information is submitted in response to the FDA order for submission of safety and effectiveness information for certain class III medical devices [Docket No. FDA-2009-M-0101], and specifically in this instance the electroconvulsive therapy (ECT) device.

1. Identification.

Electroconvulsive therapy (ECT), previously known as "shock therapy" or "electroshock therapy" is the oldest of the presently used biological treatments in psychiatry, having been first introduced into U.S. psychiatric practice almost 70 years ago. It is administered via an electroconvulsive therapy device that delivers a controlled dose of electricity to the head of an anesthetized and fully oxygenated patient to induce a generalized discharge of brain neurons lasting about a minute. This "seizure" or "convulsion" is similar to an epileptic seizure except that the muscle contractions are reduced or eliminated by muscle-relaxing medications.

During the early years of ECT before anesthesia and muscle-relaxants were introduced, dislocations, fractures, and dental damage sometimes occurred, and the experience of receiving the treatment without anesthesia caused some patients to become fearful of it. Since the introduction of modern anesthesia techniques for ECT in the late 1950s the procedure is much like any other carried out under brief anesthesia. In fact, most patients queried in one carefully done study said they preferred having ECT to a visit to the dentist (Freeman and Kendell, 1980).

The first ECT devices introduced in the U.S. in the 1940s delivered a sine-wave stimulus based on the alternating current found at wall outlets. Beginning in the late 1960s the more efficient brief pulse square wave stimulus began to replace the sine wave stimulus because it produced the same therapeutic effect with an improved safety profile, particularly with regard to memory and cognitive functioning.

Somatics' Thymatron ECT device is intended to be used in the ECT procedure by a physician to treat patients suffering from severe major depressive disorder. The Thymatron device is a free-standing, table-top medical electronic device. It includes

transformers, electronic displays, a printer, and modular circuit boards with microprocessors, memory chips, optical isolators and other electronic components, in a case. On powering up it automatically performs tests of its own integrity. It delivers a brief pulse square wave stimulus of 0.9A constant current, of maximum charge 504 mC (99.4 Joules at 220 ohms impedance) and minimum charge 5.0 mC. The Thymatron device prints the patient's electroencephalogram (EEG), electrocardiogram (ECG), pulse rate, and electromyogram (EMG, for muscle movements) during treatment on a paper strip chart that emerges from the front panel of the device.

The exceptionally careful and detailed meta-analysis of the efficacy and safety of ECT in depressive disorders performed by The UK ECT Group (2003) provides an excellent general overview and introduction to the present submission. A meta-analysis combines the results of multiple scientifically-valid studies on a subject into a single study, using a widely-accepted statistical technique. In this way it is often possible to detect effects that are hard or impossible to discern in the original studies because of too small a sample size.

The conclusions of the UK ECT Group were that real ECT was significantly more effective than simulated ECT; ECT was significantly more effective than pharmacotherapy; overall mortality was lower in patients who received ECT than those who did not; and previous ECT or total lifetime ECTs were not associated with structural brain changes.

Each of these points, as well as other related points, will be further considered below in an analysis of individual scientifically-valid studies.

2. Risks to Health.

i) The Thymatron ECT Device

Somatics' safety experience with the Thymatron ECT device

Since September 27, 1984, when FDA approved the Somatics Thymatron ECT device for marketing, more than 4,300 Thymatron devices have been sold worldwide. During that time Somatics has maintained complete safety files on the Thymatron device, including those required by the FDA's Good Manufacturing Practice regulation, the Canadian Standards Association, the German TüV testing agency, and KEMA Registered Quality. The latter three agencies regularly make on-site inspection visits to review manufacturing practices, documentation, and established quality control procedures for compliance with applicable published standards. In the ensuing 25 years there has been no occurrence of a reportable adverse event (death or serious injury) related to the use of a Thymatron ECT device, no reported occurrence of catastrophic ECT component failure, and no product recall issued.

Risk reduction with the Thymatron ECT Device

a) Risk of prolonged seizures and cardiac arrhythmias

The two most frequent complications during an ECT treatment session are excessively long seizures and irregular heart rhythms (Nuttall et al, 2004), both of which can be detected by routine monitoring during the treatment. A brain-wave monitor (electroencephalogram, EEG) enhances the safety of ECT by allowing the treating doctor to detect a prolonged seizure as it occurs so that it can be terminated with intravenous medication. Likewise, a heart monitor (electrocardiogram, ECG) allows the treating doctor to detect irregular heartbeat patterns as they occur so that they can be managed with intravenous medication. The Somatics Thymatron device includes integral EEG and ECG monitors that start recording automatically as soon as the ECT stimulus is delivered and continue until they are turned off by the doctor.

In addition to the paper EEG record the Somatics Thymatron device has an auditory EEG monitor that allows the user to tell without looking at the patient or the paper EEG whether or not the seizure has stopped. In a study of 82 consecutive ECTs the auditory EEG of the Thymatron device allowed the investigators to determine the occurrence and the duration of the induced EEG seizure with a high degree of accuracy when tested against the paper EEG standard (Swartz and Abrams, 1986).

b) Risk of excessive dose due to component failure

In the extremely rare event of catastrophic failure of an ECT device component there exists the remote possibility for an ECT device to deliver an electrical stimulus dose substantially in excess of that set by the operator, potentially causing excessive memory disturbance. To prevent such an occurrence the Somatics Thymatron device includes an independent separate redundant safety circuit that automatically measures the electrical charge at the output terminals each time the stimulus button is pressed and prevents delivery of any stimulus charge that exceeds by more than 5% that set by the operator.

To test the integrity of the electrical connection to the patient, the Somatics Thymatron device includes a static impedance test initiated by a button press. The test current is too small to be felt by a fully awake person. This test helps assure good electrode contact and prevent excessive heat release onto the skin.

Published risk assessments of the Thymatron ECT device

a) Risk of hippocampal damage

Ende et al (2000) used proton magnetic resonance spectroscopic imaging to study hippocampal effects of the Thymatron ECT device as reflected in N-acetylaspartate signals. In 17 patients receiving either unilateral or bilateral ECT (all of whom improved with treatment), no differences were found from 30 control subjects in hippocampal N-acetylaspartate signals, and thus providing no evidence for ECT-induced hippocampal atrophy or cell death.

b) Risks to everyday memory and semantic memory

The most commonly investigated potential risk of ECT concerns its possible impact on memory and cognitive functioning. Research on this risk with respect to ECT devices in

general is reviewed in Section 2.ii. below. The following study reviews this risk specifically with respect to the Thymatron ECT device.

Schatet al (2007) used a Thymatron ECT device to treat 83 DSM-IV medication free patients with unipolar depression who had been evaluated at baseline on tests of behavioral (everyday) memory and semantic memory (word fluency). One year of fie racouse of bilateralor unilateral ECT neither everyday memory scores nor semantic memory scores were reduced from baseline— in fact, bilateral ECT was associated with significantly improved semantic (but not everyday) memory scores.

It should be noted that the risk of adverse memory effects is controlled through a variety of mechanisms. It is standard clinical practice that the physician administering ECT assess the patient's mental status, including memory and cognitive functioning, before the start of the first ECT treatment and each day while the patient is undergoing treatment. If a significant adverse change in cognitive functioning is observed, the physician has several choices available to ameliorate or reduce this change, including reducing the number of treatments per week, temporarily interrupting treatment for a number of days, reducing the stimulus dose, changing the treatment electrode placement or stimulus parameter settings, changing anesthetic medications or doses, changing concurrent medications, and decreasing the total number of ECT treatments given.

ii) <u>The generic ECT device</u>

Risk of Death or Serious Injury

ECT is a safe treatment. The most recent hospital-based statistics are from the Mayo Clinic (Nuttall et al, 2004). This report described no permanent injuries and no deaths in 17,394 consecutively administered ECTs to 2,279 patients over a 14-year period.

The most recent state-based statistics are from Texas for the 5 years ending 1998 (Shiwach, Reid, and Carmody, 2001). These statistics show two deaths per 49,048 treatments. A report from California (Kramer, 1999) for the decade ending 1994, noted three deaths per 160,847 treatments. Both figures reflect the fact that receiving ECT is substantially safer than giving birth, as reflected in the most recently reported U.S. statistic of 12.1 deaths per 100,000 live births for the year 2003 (Hoyert, 2007).

Risk to the Brain

Because the brain is the intended recipient of the electrical stimulus of ECT it is necessary to consider whether ECT might conceivably cause brain injury, either directly via the electrical stimulus itself, or indirectly, via the induced seizure.

Direct brain injury from ECT could only occur through temperature elevation from heat liberated by the electrical stimulation or from cerebral anoxia occurring during the induced seizure. During the passage of the electrical stimulus for ECT the high impedance of the skull relative to the skin and subcutaneous tissues causes most of the stimulus current to be shunted through the scalp (Weaver, Williams and Rush, 1976). Considering the worst-case (i.e., smallest volume) calculation that regards the

heat generated in the brain to be evenly distributed through a cylinder of end area 20 cm^2 (the standard stimulus electrode surface area in use in the U.S.) and length of 13 cm (the typical trans-cranial distance between bitemporal stimulus electrodes), the maximum FDA-allowed output of modern brief-pulse ECT devices (100 Joules at 220 ohms impedance) would elevate deep tissue temperature by less than 0.092°C (Swartz, 1989).

Moreover, the actual brain temperature increase from an ECT stimulus is only a fraction of 0.092°C because the tissue volume through which the stimulus current passes is greatly increased by dispersion of the voltage along the scalp, and the stimulus charge greatly reduced by the aforementioned shunting through the scalp.

And, because ECT has for more than 50 years been administered concurrent with full oxygenation of the patient to consistently yield a partial oxygen pressure of at least 100 mm Hg (Posner, Plum and Van Poznak, 1969), cerebral anoxia is eliminated as a possible cause of brain injury during ECT.

Risk of brain cell injury

When brain cells are injured there are detectable increases in blood levels of a variety of proteins and protein enzymes; these can be measured before and after ECT in an attempt to determine whether ECT causes such damage.

Gillay et al (1990) measured serum levels of C-reactive protein (CRP) and several intracellular enzymes, including alkaline phosphatase (ALP), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK), before and 5min, 30 min, 4h, 1 day, 2days, and 3days after ECT in 15 consecutive patients. All concentrations remained within the normal range in every patient, except for five samples with elevated CK levels. However, because CK-MB and CK-BB fractions remained low in those samples, skeletal muscle was the presumed source of the CK elevation. These data provide no support for the possibility that ECT causes either direct brain cell leakage or a brain inflammatory response.

Zachrisson et al (1990) determined the concentrations in the cerebrospinal fluid (CSF) of three established markers of neuronal/glial degeneration: tau protein (tau), neurofilament (NFL), and S-100 beta protein, in 9 depressed patients who received therapeutic courses of ECT. Also measured was the CSF/serum albumin ratio, a reflection of potential blood-brain barrier (BBB) dysfunction. Neither levels of CSF-tau, CSF-NFL and CSF-S-100 beta protein, nor the CSF/S albumin ratio, were significantly changed by ECT, providing no biochemical evidence of neuronal/glial damage or BBB dysfunction following a therapeutic course of ECT.

Berrouschot et al (1997) measured serum neuron-specific enolase (NSE), a sensitive marker of neuronal damage, in 7 patients with major depressive disorder who were treated with ECT for the first time. ECT was administered every 2days, three times a week under standard conditions and blood samples were drawn at the following times. For the first ECT: 15 and 1 min before ECT, and 1, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120 min, and 8, 12, 24h after ECT. For all subsequent ECTs: 1 min before and 4h after every ECT. After an average of 10 ECTs per patient, there was no difference in serum NSE levels before and at all times following the first ECT, nor were any differences found in serum NSE levels before and after each subsequent ECT, indicating that ECT does not cause neuronal damage.

Myelin basic protein is an antigen that constitutes 30% of the myelin sheath, and its immunoreactivity in serum and cerebrospinal fluid correlates with the degree of central nervous system damage that occurs with stroke and cerebral trauma. Hoyle, Pratt, and Thomas (1984) found no difference in serially sampled serum myelin basic

protein immunoreactivity between a sample of 13 patients undergoing ECT and a sample of 14 normal controls, nor was any pre- to post-ECT increase in mean reactivity observed in the patient sample.

Risk of brain structural damage

Magnetic Resonance Imaging (MRI) provides a clear opportunity for non-invasive high-resolution viewing of brain structure in patients receiving ECT.

Coffey et al (1991) blindly-analyzed serial MRIs obtained before and after treatment and at 6-month follow-up in 35 depressed patients receiving courses of brief-pulse bilateral ECT. No acute or delayed changes in brain structure were found, as measured by alterations of the total volumes of the lateral ventricles, the third ventricle, the frontal lobes, the temporal lobes, or the amygdala-hippocampal complex. In five subjects, pairwise global comparisons revealed an apparent increase in subcortical hyperintensity, which the authors interpreted as most likely reflecting progression of ongoing cerebrovascular disease during follow-up.

Risk of creating an epileptic focus in the brain

It has been suggested on hypothetical grounds that the repeated seizure inductions of ECT might create ("kindle") a permanent epileptic focus in the brain of some patients receiving this treatment. Ethical considerations prohibit the study of human brain kindling, so the relevant data must come from animal studies.

Kraghet al (1994) implanted electrodes in the amygdalae of 32 rats that were then randomly allocated to receive 12 weekly genuine or sham electroconvulsive shocks (ECS). Three months after the last ECS, kindling was initiated artificially in all the rats by daily stimulation via the implanted electrodes: rats pretreated with genuine ECS did not kindle faster than sham ECS-treated rats— in fact, rather than a facilitated development of kindling following ECS, a statistically significant inhibition of kindling was found in the genuine ECS group.

Post et al (1984) demonstrated a marked protective effect against kindling lasting up to 5 days after a 7-day course of once-daily ECS in rats. Moreover, when ECS was administered before the stimulation given to induce kindling, this phenomenon was completely blocked.

Considering the potent antikindling properties of ECS in rodents, it is highly unlikely that ECT causes kindling in man.

Risk of persistent or permanent memory loss

All forms of ECT are capable of causing immediate adverse effects on memory shortly after each individual treatment and after a course of treatments, and some of the clinical approaches to ameliorating such adverse effects are outline in the last paragraph of section 2.i above. The question is whether any of these short-term memory effects are detectable as long as 6 months after the final treatment, which is the generally-accepted interval for classifying such memory changes as "persistent" rather than "temporary".

Memory (amnestic) effects of ECT consist of two main types: anterograde, for events occurring after a treatment or course of treatments, and retrograde, for events occurring just before the first treatment, or for personal (autobiographical) and public events occurring during the weeks, months, or years before the first treatment. The studies reviewed below are limited to the stimulus wave-form of ECT now exclusively used in

virtually all U.S. hospitals—the brief pulse, square-wave stimulus. Further, it should be noted that this review only considers the effects of bilateral (i.e., bitemporal or bifronto-temporal) treatment electrode placement, the method that invariably produces the more pronounced immediate anterograde and retrograde memory effects in every published comparison. If persistent amnesic effects are not detectable after bilateral ECT, they will not be detectable after any other form of ECT either.

Lisanby et al (2000) randomly assigned 55 patients with major depressive disorder to low- or high-dose right unilateral or bilateral ECT and tested them at baseline on memory batteries containing both autobiographical and public events. Two months after ECT these investigators did not find statistically significant (p<0.) worsening of either autobiographical or public event memory for either form of ECT at either dosage level.

Calev, Nigal, and Shapira (1991) administered a comprehensive test battery of memory and other cognitive functions to 27 medication free patients with major depression before and shortly after a mean course of 9 bilateral, brief-pulse ECTs administered according to a dosage titration procedure. They reexamined 14 patients 1 month and 6 months after the conclusion of the treatment course. Anterograde memory was significantly impaired immediately following the course of ECT, but at 1 month follow-up, performance had improved to pre-ECT levels and exceeded them at the 6 month follow-up.

Calev, Nigal, and Shapira (1991) also included retrograde memory tests for autobiographical and public events using a test battery that covered the period of several years prior to ECT. Although significant impairment for autobiographical (but not public) events was recorded immediately following a course of ECT, this impairment had disappeared 1 month later, followed by improvement over baseline shown at the 6 month test interval.

Sackeim et al (1986, 1987b) employed a variety of recall and recognition tests for words, shapes, and faces that had to be learned 15 minutes prior to brief-pulse, just-above-threshold unilateral or bitemporal ECT. Patients were retested immediately after orientation had returned, at which time no retrograde amnesic effects were detected and improvement over baseline was recorded on one of the retrograde memory tasks. Of course, if retrograde amnesia was not detected immediately after ECT, it could not persist afterwards. This fact was confirmed by Sackeim et al (1991.) in a follow-up study in which autobiographical memory assessments prior to ECT showed no decrements 2 months after a course of either just-above-threshold or 2.5 times threshold bitemporal ECT.

Thus, follow-up studies up to 6 months after a course of bilateral brief-pulse square-wave ECT find no evidence for persistent anterograde or retrograde amnesia.

3. <u>Recommendation.</u>

Somatics believes the ECT device should be reclassified into class II because special controls, in addition to general controls, will provide reasonable assurance of safety and effectiveness. There presently exists sufficient information to recommend the following specifications based on almost 70 years' safe and effective use of ECT devices in the U.S.

brief pulse, square wave stimuli
All published studies report the brief pulse, square wave stimulus to be more efficient at seizure induction than the sine wave stimulus, achieving the same therapeutic effect with significantly less memory and cognitive disturbance. Typical parameter settings are in the ranges of pulsewidth 0 to 1.5 ms, frequency 0 to 140 Hz, and total stimulus duration 0 to 8 sec.

constant current stimulus output
A constant current ensures delivery of a specified charge (in millicoulombs, mC) at each stimulation, whereas with constant voltage the charge delivered varies with the skin impedance of the patient, which can change from day to day.

maximum energy dose 100 J@ 220 ohm impedance
This is the present electrical energy dosage limitation of U.S.-made ECT devices, based on recommendations made to FDA in 1982 by the American Psychiatric Association in its failed *Petition to Reclassify ECT Devices* to Class II. However, it should be considered that several U.S.-based ECT investigators (Sackeim, 1991; Krystal, Dean, and Weiner, 2000; Abrams, 2001) have recommended a higher maximum electrical dose in order to be able to treat the large and increasing number of older patients with major depression, who have much higher than average seizure thresholds. Moreover, other English speaking countries (e.g., U.K., Australia) have allowed ECT devices to be marketed with double the output of U.S. devices: 200J @ 220 ohms impedance. In fact, the U.K. has made that particular higher maximum dose mandatory for all ECT devices sold there.

pretreatment stimulus electrode impedance test
A test of impedance of the electrode-to-skin interface employing a current too small to be felt by a fully awake person helps assure good contact and prevent skin burns. Typical clinical measures routinely used to lower skin impedance and thus also reduce the risk of skin burn include increasing pressure on the stimulus electrode(s), cleaning the skin and applying a conductive gel or solution, repositioning the electrode(s), and gently abrading the skin under the electrode(s) as with an emery board.

treatment electrode surface area no less than 20 cm^2
In order to prevent excessive heat liberation at the electrode-to-skin interface and possible resultant skin burns, the temperature at the electrode-to-skin interface should not exceed 50 deg. C. This constraint is reliably achieved if the stimulus electrode surface area is no smaller than 20 cm^2.

independent dosage output monitoring and controlling circuit
As described in 2i(b) above, this circuit repeatedly tests the dose at the output terminals and aborts stimulus delivery if the output exceeds the user-set dose by more than 5%.

two channel EEG monitor
Being able to assess for continuing cerebral seizure is important for preventing the memory and cognitive risks of prolonged seizures. Because paroxysmal seizure activity can persist in the brain after all visible muscle movements have ceased, the EEG is necessary for monitoring for continuing seizure activity and for assessing the efficacy of any intravenous anticonvulsant medications administered to terminate a prolonged seizure. Moreover, because a generalized brain seizure involving both hemispheres is considered necessary for the full therapeutic effect of ECT, two channels of EEG monitoring are needed to ensure that the induced seizure is not limited to one hemisphere.

stimulus charge display
To avoid delivery of a stimulus charge different from the one intended, the stimulus charge selected by the user should be on display when stimulus delivery is initiated.

labeling
WARNING: HAZARDOUS ELECTRICAL OUTPUT, READ USER'S MANUAL BEFORE OPERATING. FOR USE ONLY BY A LICENSED PHYSICIAN PRIVILEGED TO ADMINISTER ECT. A COPY OF THE USER'S MANUAL SHOULD BE IMMEDIATELY AVAILABLE WHEN THIS DEVICE IS IN USE.

4. Summary of Reasons for Recommendation.

The Somatics Thymatron ECT device has already been in functional class II during its entire lifetime of 25 years, during which its safety and effectiveness have been demonstrated as outlined above and in paragraph 5 below.

For the last 20 years the Thymatron device was certified by the German testing agency TüV to IEC 60601.2.14, the internationally-accepted mandatory performance standard for the ECT device. That particular performance standard was withdrawn several years ago, leaving only the general standard for electromedical devices, IEC601.1, which the Thymatron device also meets.

Since 1998 the Somatics Thymatron ECT device been subject to the special controls of post-market surveillance and vigilance as monitored and certified by KEMA Registered Quality, to the International Organization for Standardization (ISO) 9002 consensus standard. KEMA has included in its survey all Thymatron devices sold in the U.S., and FDA has historically incorporated international ISO consensus standards into special controls guidance documents for the purpose of reclassifying certain class III devices (e.g., the kneejoint patellofemorotibial prosthesis) to class II (Federal Register, 2003). KEMA is also one of the organizations accredited by FDA to conduct inspections of class II and class III manufacturing establishments.

5. Summary of valid scientific evidence on which the recommendation is based.

Efficacy of the Thymatron ECT Device

Scientifically-valid investigations across 4 countries in well over 600 patients found patients with major depression who were treated with a Thymatron ECT device enjoyed substantial, objectively-measured improvement in the relatively narrow range of 67% to 95%.

Williams et al (2000) used a Thymatron ECT device to administer 1.5 times threshold bitemporal ECT to 15 patients with DSM-IV unipolar major depression, obtaining a 67% reduction in Hamilton Depression scale scores at the end of their course of treatment.

Ranjkesh, Bajekatain, and Akuchakian (2000) randomly assigned 39 DSM-IV patients with major depression to receive courses of 8b frontal, bitemporal, or right unilateral ECT administered with a Thymatron ECT device.

Blindly-obtained Hamilton Depression scale ratings at baseline and after the 8th ECT revealed 73% improvement for the entire sample, with no significant difference among the treatment groups.

Kho et al (2004) conducted a retrospective chart review study of the response of 57 patients with DSM-IV unipolar major depression to treatment with a Thymatron ECT device using age-based dosing. Hamilton Depression Scale scores obtained before and after a mean course of 7.2 ECTs showed 70.4% improvement, with a 67% remission rate achieved across the entire sample.

Heikman et al (2004) used a Thymatron ECT device to treat 24 DSM-IV patients with major depression who were randomly assigned to high-dose right unilateral ECT, moderate-dose right unilateral ECT, or low-dose bifrontal ECT. Blindly-obtained Hamilton Depression scale scores at baseline and after the ECT course showed an overall 66% improvement, with the best improvement (73%) recorded for the high-dose right unilateral group.

In the multi-hospital NIH funded CORE study Petrides et al (2001) used Thymatron ECT devices to treat 253 patients with unipolar major depression with bilateral ECT at 1% above threshold. The overall remission rate for the sample as determined by blindly-obtained Hamilton Depression Scale ratings was 87%, with patients with psychotic depression enjoying a remarkable 95% remission rate, compared with 82% for patients with non-psychotic depression.

Abrams, Swartz, and Vedak (1991) conducted a random-assignment, double-blind, controlled comparison of the antidepressant potencies of fixed-high-dose (378mC) right and left unilateral ECT using a Thymatron ECT device in 30 patients who satisfied criteria for major depression with melancholia, of whom 19 received right-sided and 11, left-sided, ECT. Depression ratings were blindly obtained at baseline and immediately following the 3rd and 6th ECTs. Patients receiving left unilateral ECT showed an 83% improvement after 6 treatments, compared with only 70% for right unilateral ECT. Although this main treatment effect difference was not significant, post-hoc testing did show a significant advantage for left unilateral ECT from the 3rd to 6th treatments: left unilateral ECT worked faster later in the course.

Efficacy of ECT in general

Data from scientifically valid studies using the form of ECT (bitemporal) generally associated with the highest response rates demonstrate it to be a highly effective treatment for depression. The following table shows the results for bitemporal ECT only of the 6 large studies published in the modern era using structured diagnostic evaluation, systematic blind outcome assessment on a reliable observer-administered depression rating scale, and brief-pulse, square wave stimuli with specified dosage. The response rates achieved vary in a narrow range from 70% to 87.8% with a mean of 83.7% and demonstrate the reliably high efficacy of ECT in the treatment of depression.

RESPONSE RATES WITH BITEMPORAL ELECTROCONVULSIVE THERAPY

Study	Sample size	No. of responders	Response rate (%)
Kellner et al., 2006	394	346	87.8
McCall et al., 2002	37	27	73
Abrams et al., 1991	18	14	77.8
Sackeim et al., 1987a	27	19	70.4
Sackeim et al., 1993	50	35	70
Sackeim et al., 2000	50	16	80
Total	*546*	*457*	*83.7*

Since none of the studies included a sham- or drug-treated control group, however, the question arises whether this apparent efficacy might be merely a placebo effect.
To clarify this point it is necessary to review several types of studies: Genuine vs. sham ECT in depression; ECT versus other FDA-approved treatments for depression (antidepressant drugs and transcranial magnetic stimulation); and comparisons of different forms of ECT in depression

1. <u>Genuine vs. Sham ECT in Depression</u>

The following sham ECT studies all satisfy strict methodological requirements, including random assignment to treatment groups and double-blind, objective, outcome assessments.

Freeman, Basson, and Crighton (1997) treated 10 patients with primary depression with either 2 genuine (bilateral, partial sine-wave) or 2 simulated ECTs during their first two weeks of treatment, after which all patients received genuine bitemporal ECT for the remainder of the course. Mean scores on the Hamilton, the Wakefield, and the Visual Analogue depression scales after the first 2 treatments were significantly lower after genuine than after sham ECT, and patients in the sham ECT group ultimately received significantly more treatments prescribed by clinicians who were blind to group assignment.

Lambourn and Gill (1978) assigned 32 patients with psychotic depression to receive either 6 brief-pulse, ultra low-dose (only 10 joules) unilateral ECTs or an equal number of identical anesthesia inductions without the passage of electricity. Mean Hamilton rating-scale scores obtained 24 hours after the sixth treatment did not differ significantly for the 2 groups.

In the Northwick Park ECT trial Johnstone et al (1980) gave 70 patients with endogenous depression a 4-week course of 8 sine-wave bitemporal ECTs or 8 anesthesia inductions without electrical stimulation. Mean Hamilton depression scale scores after 4 weeks were significantly lower in the genuine ECT group by about 26 points. The advantage of genuine over sham ECT in this study was most marked in the subgroup of patients with delusional depression (Clinical Research Centre, 1988), the most severely ill of all patients with depression.

West (1981) treated 22 patients with primary depression with courses of 6 genuine or 6 sham ECTs. The patients were blindly rated on both doctors' and nurses' rating scales, and were then switched to the alternate treatment if indicated. There was a highly statistically significant and clinically important improvement in the genuine compared with the sham ECT group, and 10 out of 11 sham ECT patients (but no genuine ECT patients) were switched to the alternate method, from which they derived the expected degree of improvement.

In the Leicestershire trial, Brandon et al. 1984 studied 95 patients with major depression who were allocated to up to 8 genuine bitemporal sine wave ECTs or 8 sham ECTs. A significantly greater improvement in Hamilton depression scale scores was seen in the genuine compared with the sham ECT group at 2 and 4 weeks. As in the Northwick Park trial above, the largest genuine ECT advantage occurred in the most severely ill patients— the subgroup of patients with delusional depression.

In the Nottingham ECT study, Gregory, Shawcross and Gill (1985) randomly assigned 60 patients with depression to sine-wave ECT with bitemporal or unilateral placement or to sham ECT. Both genuine methods were superior to sham ECT after 2, 4, and 6 treatments, as measured by the blindly-administered Hamilton and Montgomery-Asberg depression scales.

Thus, 5 out of 6 scientifically valid studies of simulated compared with real ECT in the treatment of depressive illness show both a statistically significant and clinically

substantial advantage for genuine ECT in reducing depression scale scores during and immediately following the treatment course.

It is not surprising that the single study (Lambourn and Gill, 1978) that failed to show an advantage for real compared with sham ECT differs from all the others in having used brief-pulse, ultra low-dose (10 J) unilateral ECT as the "active" treatment. A similar low-dose technique using an even higher stimulus energy (mean = 18 J) was shown by Sackeim et al. (1987a) to be clinically ineffective for right unilateral ECT, the same application used by Lambourn and Gill (1978). Subsequent studies (e.g., Abrams, Swartz, and Vedak, 1991) amply demonstrated that unilateral ECT must be administered with high stimulus dosing to maximize efficacy.

Following a successful course of ECT it is standard practice to prescribe maintenance antidepressant medication to prevent relapse, for example with nortriptyline, lithium, or both. If this fails, continuation ECT may be tried, in which patients continue to receive an outpatient ECT treatment every 1 to 4 weeks. A problem with most of the efficacy studies reviewed above is that patients typically receive either no post-ECT maintenance therapy, or receive a variety of "doctor's choice" treatments, including both ECT and drugs, administered non-systematically. So it is also not surprising that evaluations performed weeks or months after completion of the acute ECT treatment course usually fail to show a significant advantage for ECT.

2. <u>ECT vs. Other FDA-Approved Treatments for Depression</u>

ECT versus Antidepressant Drugs

Folkerts et al (1997) randomly assigned 39 patients with major depression to receive either 2.5 times threshold unilateral ECT (N = 21) or treatment with the FDA-approved antidepressant paroxetine (N = 18). After 4 weeks there was a substantial and highly significant advantage for ECT over paroxetine: a 59% reduction in blind-rater-obtained Hamilton Depression Scale score for the ECT group, compared with only 29% for the paroxetine group.

Gangadhar, Kapur, and Kalyanasundaram (1988) studied 24 patients with primary endogenous depression who were randomly assigned to receive a course of genuine bilateral or sham ECT in conjunction with either placebo capsules or imipramine, 150 mg/day. The first 6 treatments were given over 2 weeks, after which genuine ECT plus placebo was found to be significantly superior to sham ECT plus imipramine in lowering blind-rater-obtained Hamilton depression scale scores. This neatly demonstrated the efficacy of genuine versus sham ECT as well as the superior efficacy of ECT over imipramine.

In a retrospective chart-review study Gagne et al (2000) identified 29 patients who received continuation ECT + antidepressant medication and compared them with 29 carefully-matched control patients who received only continuation antidepressants after initially responding to a course of ECT. Over a 4-year follow-up period the outcome was significantly better in the ECT + antidepressants group (93% likelihood of continuing without relapse or recurrence) than in those who received antidepressants alone (53% likelihood of continuing without relapse or recurrence).

ECT vs. Transcranial Magnetic Stimulation (TMS)

TMS, in which a magnetic field is applied to the head, is an FDA-approved treatment for major depression.

Brantie tal (2007) randomly assigned 46 patients with DSM-IV major depression to receive either a 15-day course of TMS to the left dorsolateral prefrontal cortex (n = 24) or a doctor's choice course of ECT delivered at 1.5 times seizure threshold (n = 22). Blindly-obtained Hamilton Rating Scale Depression scores at baseline and at the end of the treatment course showed significantly greater improvement in the ECT group, with 13 (59%) achieving remission compared with only four (17%) in the TMS group.

3. Comparison of different Forms of ECT in Depression

Proof of the efficacy of a given treatment is not limited to studies comparing that treatment with placebo or alternative approved active treatment. So long as scientifically valid methods are employed, efficacy can be demonstrated by studies that compare two different forms of a particular active treatment and find one form superior to the other.

One standard procedure for determining the stimulus dose for ECT requires preliminary testing of the patient's threshold for developing a seizure and then administering a stimulus dose at a particular multiple of that threshold. An alternate method administers a fixed stimulus dose, set high enough to ensure a well-developed seizure on the first application.

Moderately Suprathreshold vs. Fixed High-dose Unilateral ECT in Depression

McCall et al (2000) randomly assigned 72 patients with major depressive disorder to receive right unilateral ECT at either a moderately suprathreshold dose (mean = 1.36 millicoulombs, mC) or a fixed high dose of 40 mC. After an average course of 5.7 ECTs 67% of the patients receiving fixed high dose ECT responded, compared with 35% of those who received moderately suprathreshold dosing (p=0.), thus demonstrating the efficacy of fixed, high-dose ECT in the treatment of major depression.

In bilateral (bitemporal) ECT, one treatment electrode is placed on each temple, whereas in unilateral ECT both treatment electrodes are placed over the same side of the head, almost invariably the right hemisphere. Although it is abundantly clear that unilateral ECT is associated with fewer adverse memory effects than bilateral ECT, it remains to be determined whether unilateral ECT is clinically as effective.

Bitemporal vs. Right Unilateral ECT in Depression

Sackeim et al (1987) conducted a double-blind, random-assignment study comparing the relative efficacy of bitemporal and right unilateral ECT, both administered with just-above-threshold dosing. The two conditions did not differ in the duration of generalized seizures or in the number of treatments administered to achieve clinical response. In 52 patients with primary major depressive disorder, bilateral ECT was markedly and significantly superior to right unilateral ECT in reducing blindly-obtained Hamilton Rating Scale scores for depression, thus demonstrating the efficacy of just-above-threshold bitemporal ECT as a treatment for major depression.

4. Comparison of Different Forms of ECT in Depression

Proof of the efficacy of ECT can also come from scientifically-valid studies that demonstrate a differential response rate to ECT of different forms of the same illness. Demonstrating that one form of an illness responds significantly better to ECT than another confirms the efficacy of ECT in the responsive form.

In the study of Petrides et al (2001) cited above, patients with psychotic depression (ie, uniformly severe major depression) exhibited a significantly greater remission rate with bilateral ECT than patients with non-psychotic depression, thus demonstrating that bilateral ECT is an effective treatment for major depression that is so severe it is psychotic.

Thus, numerous and varied scientifically valid studies in patients with major depression provide a definitive answer to the question raised in the opening paragraph of this section as to whether the reported great efficacy of ECT might be only a placebo effect: it clearly is not. The data summarized above demonstrate that ECT is a reliable and substantially efficacious treatment for major depression, and that its results in treating this disorder compare very favorably with other FDA-approved treatments for major depression, especially when severe.

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