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EXHIBIT 1

FDA Executive Summary

Prepared for the
January 27-28, 2011 meeting of the
Neurological Devices Panel

Meeting to Discuss the Classification of Electroconvulsive Therapy Devices (ECT)

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Draft Executive Summary

Electroconvulsive Therapy (ECT) devices induce seizure by applying electricity to the scalp and are used "for treating severe psychiatric disturbances (e.g., severe depression)." *See* 21 CFR 882.5940. These devices were legally marketed in the United States prior to the Medical Devices Amendments of 1976. Although classified into Class III, the highest risk-based classification for devices, FDA has not yet established a requirement for premarket approval (PMA) to affirmatively demonstrate a reasonable assurance of safety and effectiveness. ECT devices have instead been regulated through the premarket notification [510(k)] regulatory pathway, which requires a showing of substantial equivalence to a legally marketed device and is usually reserved for intermediate and low risk devices.

In January 2009, the Government Accounting Office (GAO) recommended that the FDA take steps to issue regulations for class III device types currently allowed to enter the market via the 510(k) process (including ECT devices) by either requiring PMAs or reclassifying them into Class I or Class II [GAO-09-190].

On April 9, 2009, FDA issued a Federal Register Notice [Docket No. FDA-2009-M-0101] requesting safety and effectiveness information from manufacturers to determine whether ECT devices should remain in Class III, requiring PMAs, or whether they should be reclassified into Class I or II. A subsequent notice [Docket No. FDA-2009-N-0392] requested public comment on the classification of ECT devices.

To assess safety and effectiveness of ECT devices, FDA has conducted an independent, comprehensive, systematic review of the scientific literature and when possible, has performed meta-analyses of safety and effectiveness using studies satisfying the most rigorous data criteria (e.g. randomized controlled trials). This executive summary presents a brief clinical background, regulatory considerations, FDA review methodology, review of public and manufacturer dockets, safety review of the literature, effectiveness review of the literature, and potential mitigating factors of specific risks for ECT devices.

The purpose of this advisory panel meeting is to supplement FDA's review with expert recommendations regarding the appropriate classification of ECT devices. The discussion will include discussion of the safety and effectiveness of ECT devices, and whether sufficient information exists to develop special controls to adequately mitigate the risks of ECT to support reclassification into Class II.

1. Clinical Background

The ECT procedure was first conducted in 1938 (Rudorfer et al, 1997). Two Italian physicians, Ugo Cerletti and Lucio Bini, guided by a theory holding an antagonistic relationship between seizures and psychosis, became the first to use electricity to induce a therapeutic seizure in humans Faedda et al. 2009. They reported on the first treatment of a patient using this method in 1939 (Bini 1995). Joining a number of other somatic-based therapies of the era (prior to the advent of modern pharmacotherapy), ECT became a popular intervention for psychiatric conditions.

Since that time, the use of ECT has waxed and waned. In the 1950's and 60's, with the development of drug therapies for psychiatric conditions, and due to concern for serious device-related adverse events, the use of ECT in the U.S. declined (Lisanby 2007). However, in recent years, interest in, and use of, ECT has experienced a resurgence; ECT use in the U.S. has been estimates at 100,000 individuals receiving this treatment annually (Hermann et al. 1995). Reflecting the greater proportion of women who suffer from major depression, two-thirds of patients who receive ECT are women (Olfson et al. 1998). In clinical practice, ECT is generally considered after failure of one or more antidepressant medication trials, or when there is need for a rapid and definitive response (APA 2001; p. 23-24).

ECT has been used to treat a variety of psychiatric disorders. These disorders include:

- Depression (unipolar and bipolar)
- Schizophrenia
- Bipolar manic (and mixed) states
- Catatonia
- Schizoaffective disorder

The evidence supporting the effectiveness of ECT for each of these indications is variable and will be reviewed in Section 5 of this executive summary.

Potentially significant adverse events have also been associated with ECT including physical trauma, fractures, cardiac ischemia, cardiac arrhythmias, prolonged apnea and even death. With the use of general anesthesia, neuromuscular blocking agents, and modern cardiopulmonary management techniques (i.e., mechanical ventilation, monitoring, cardiovascular medications) during the administration of ECT, most of these adverse events have been significantly reduced. Still, the risk of these adverse events is not completely eliminated, and other adverse events are also of concern. Other adverse events include:

- Cognitive dysfunction (including memory loss)
- Post-treatment confusion
- Prolonged seizures
- Treatment-emergent mania
- Exacerbation of psychiatric symptoms and/or negative subjective reactions
- Headache
- Muscle soreness
- Nausea and vomiting

One of the most concerning adverse events reported with ECT is memory loss. ECT has been associated with various types of memory loss, including both anterograde and retrograde memory loss. Particular concern has been reported about the risk of retrograde autobiographical memory loss with ECT treatment (Lisanby 2007). Adverse events of ECT will be examined in more detail in the section on the safety of ECT presented in Section 4.

Finally, given the potential risks associated with ECT, the issue of informed consent is also an important consideration with this treatment. Informed consent procedures should ensure that the potential risks and benefits are clearly conveyed to the patient (or his/her legal guardian), so that the patient may make an informed decision about whether to undergo the procedure or not. Critics have charged that informed consent procedures for ECT are inadequate (Breeding 2000; Ross 2006).

2. Regulatory Considerations

2.1 Risk-Based Classification and Regulation of Devices

The Medical Device Amendments to the Food, Drug, and Cosmetic Act were enacted in 1976. These amendments categorized device types into one of three classes (Class I, II, or III) based on risks posed by the device.

Class I devices are devices for which general controls alone are sufficient to assure the safety and effectiveness of the device. They are generally low risk devices and need only conform to general controls to provide reasonable assurance of safety and effectiveness. The provisions of general controls include prohibition of adulterated/misbranded devices, manufacturer registration and listing requirements, good manufacturing practices, and record keeping. Most Class I devices are exempt (subject to limitations defined in the regulations) from premarket notification [510(k)].

Class II devices are those devices for which general controls, alone, are insufficient to assure safety and effectiveness, and additional existing methods are available to provide such assurances. Therefore, Class II devices are also subject to special controls in addition to the general controls of Class I devices. Special controls may include special labeling requirements, design requirements, mandatory performance standards, and postmarket surveillance requirements (e.g., patient registries, device tracking requirements). In order to market most Class II devices, manufacturers must submit a premarket notification [510(k)] submission, in which the manufacturer compares their device to a legally marketed predicate device. A predicate device may be one of the following:

- A device already marketed in the United States prior to May 28, 1976 (a pre-amendments device);
- A device found by FDA to be Substantially Equivalent;
- A reclassified device; or,
- A device classified by a de novo petition

A 510(k) requires demonstration of "substantial equivalence" to a predicate device. A device is deemed substantially equivalent to a legally marketed device if it:

- Has the same intended use, and
- Has the same technological characteristics as the predicate device

or

- Has the same intended use, and
- Has different technological characteristics but the information in the 510(k):
    - Does not raise new types of questions of safety or effectiveness, and
    - Performance data demonstrate that it is as safe and as effective as the predicate device.

Class III devices are defined as those devices for which insufficient information exists to assure their safety and effectiveness solely through general or special controls. They often support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury. Class III devices require Premarket Approval (PMA) before they can be legally marketed.
This process of scientific review is required in order to provide reasonable assurance of safety and effectiveness of Class III devices. PMA approval is based on a determination by FDA that the PMA submission contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s). Post-approval studies may be required as a condition of PMA approval in order to provide additional long-term data.

2.2 Class III Preamendments Devices and Section 515(i)

Devices that were in existence prior to the Medical Device Amendments of 1976 are referred to as "preamendments devices." Because FDA did not establish the requirement for PMA at the time of classification, some preamendment devices classified into Class III have been regulated through the premarket notification 510(k) pathway. ECT is one of 26 such remaining preamendments device types that are often referred to as "Class III preamendments" devices.

Section 515(i) of the Safe Medical Devices Act of 1990 directed FDA to either revise the classification of these devices into class I or II or require the device to remain in class III; and for devices remaining in class III, to establish a schedule for the promulgation of a rule requiring the submission of PMAs for the device.
[http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm110198.htm]

Subsequently, in January 2009, the Government Accounting Office (GAO) also recommended that the FDA take steps to issue regulations for class III device types currently allowed to enter the market via the 510(k) process (including ECT devices) by requiring PMAs or reclassifying them to a lower class [GAO-09-190].

On April 9, 2009, FDA issued a Federal Register Notice [Docket No. FDA-2009-M-0101]) requesting safety and effectiveness information from manufacturers to determine whether ECT devices should remain Class III devices, requiring premarket approval (PMA), or whether they should be reclassified into Class I or II.
[http://www.regulations.gov/search/Regs/home.html#documentDetail?R=090000648094bbd0]

Currently there are two manufacturers marketing devices in the U.S.: MECTA and Somatics. Both manufacturers responded to the Federal Register Notice and provided information on their respective devices. The complete manufacturers' submissions can be found at:
[http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2009-M-0101].

In addition, on September 10, 2009, FDA issued Federal Register Notice [Docket No. FDA-2009-N-0392] announcing the opening of a public docket to receive information and comments regarding the current classification efforts related to ECT devices.
[http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480a20202]
The docket closed on January 9, 2010 after receiving 3,045 responses. Complete access to all responses to the public docket can be found at:
http://www.regulations.gov/search/Regs/home.html#advancedSearch; enter FDA-2009-N-0392.

In addition to the responses obtained from manufacturer and public dockets, FDA will carefully consider recommendations from the Neurological Devices Advisory Panel regarding the most appropriate classification (Class I, II, or III) for the ECT device type.

2.3 ECT Device Regulatory History

ECT devices were legally marketed in the United States prior to May 28, 1976, and therefore, are preamendments devices. Although they are, by regulation, Class III devices, they are currently regulated under the 510(k) process. In the Code of Federal Regulations, ECT devices are described in 21 CFR §882.5940:

> Electroconvulsive therapy device.
>
> (a) *Identification.* An electroconvulsive therapy device is a device used for treating severe psychiatric disturbances (e.g., severe depression) by inducing in the patient a major motor seizure by applying a brief intense electrical current to the patient's head.
>
> (b) *Classification. Class* III
>
> (c) *Date PMA or notice of completion of a PDP is required.* No effective date has been established of the requirement for premarket approval. See 882.3.

In the United States, there have been nine 510(k) applications cleared for ECT devices from four different manufacturers. Table 1, located in the appendix, describes each 510(k) submission (see p. 55). Indications for use (IFUs) for cleared ECT devices have included: severe depression,

major depressive episode with melancholia, schizophrenia, bipolar disorder-depressed phase, bipolar disorder-manic phase, catatonia, schizophreniform and schizoaffective disorder.

The Panel will be asked to consider if there is sufficient data upon which to develop adequate special controls for mitigating risk for each of the following indications:

a. Depression (unipolar and bipolar)
    i. First-line treatment
    ii. Treatment resistant
b. Bipolar manic (and mixed) states
c. Schizophrenia
d. Schizoaffective disorder
e. Schizophreniform disorder
f. Catatonia

3. FDA Review Methodology

FDA conducted a comprehensive review of scientific literature to assess the safety and effectiveness of ECT devices. Analyses of FDA's review will contribute to the determination of whether ECT devices should remain as Class III devices with the new requirement for pre-market approval (PMA), or be reclassified as Class II devices subject to the premarket notification [510(k)] regulatory pathway.

The information considered in the review was obtained from a variety of sources. These sources include:

- Manufacturer docket submissions
- Public docket submissions
- Manufacturer and User Facility Device Experience database
- FDA independent literature review

The two manufacturer submissions have been reviewed and information contained in the responses (particularly with regard to adverse events) is presented in 4.2. The public docket received 3,045 responses. These responses have been analyzed and a summary is presented in 4.1. In addition to the responses to the two Federal Register Notices, FDA maintains a Manufacturer and User Facility Device Experience (MAUDE) database. This database contains adverse event reports submitted to FDA from manufacturers, user facilities and other external sources. As of December 7, 2010, the MAUDE database has received 151 original reports. These reports are summarized in 4.3.

While FDA considers information obtained from responses to Federal Register Notices and MAUDE reports critical to the review of ECT devices, it is important to recognize the limitations of such information (i.e., information is not systematically obtained, and frequency of events cannot be assessed given lack of information on the entire population in question). Because it is likely that MAUDE does not represent a comprehensive listing of all adverse events that have been associated with ECT, it may not be representative of general clinical practice. Additionally, both the public docket and manufacturer docket solicited information from external sources in an

uncontrolled manner. While some reports appear to be substantiated with evidence supplied in the response, many reports do not. Similar to the MAUDE database, it is unclear how representative responses to the public and manufacturer docket are of general clinical practice. Because it is unclear if the responses are derived from a defined population (e.g., ECT recipients), this information cannot be used to establish estimates of occurrence. Still, these reports can be interpreted as indicators of the general experience of ECT in the U.S., and serve to identify what areas of concern do exist. Additional information (i.e., data from case studies, case series, retrospective studies, observational studies, and controlled trial, and information from comprehensive reviews) from the published literature has been examined in order to gain a more detailed understanding of the occurrence and severity of potential adverse events.

Through this process, significant potential adverse events were identified; these adverse events became the subject of a comprehensive analysis to characterize the associated risk and any potential mitigating factors. In order to satisfy the regulatory requirement for valid scientific evidence to "consist principally of well-controlled investigations" [21 CFR 860.7(e)(2)], and guided by docket submissions and adverse events reports, this part of the review consisted of an independent FDA review of the scientific literature on specific risks and effectiveness of ECT. The review team made a decision to conduct the FDA systematic review and meta-analysis utilizing data solely from randomized controlled trials (RCTs), given the significant body of existing literature published on ECT and the regulatory directive to rely principally on "well-controlled investigations." Titles were identified using a systematic search strategy, as well as a review of docket submissions, and cross-referencing of reference lists from published practice guidelines, systematic reviews, and meta-analyses.

The literature search was conducted by searching PubMed, CINAHL and PsycINFO for all studies published through September 7, 2010. In order to gain additional information about potential adverse events, the search strategy included all studies reporting on safety and effectiveness of ECT (not only RCTs). Search terms were included as both text and MESH headings and included the following: "major depression" "electroconvulsive therapy", "bipolar depression", "schizophrenia", "schizoaffective psychosis", "schizoaffective disorder", "catatonia", "mania", and "mixed states." Studies were limited to English, human, clinical trial, Cochrane review, controlled clinical trials, meta analyses, randomized controlled clinical trials, systematic reviews, research study, cohort study, case-control study, cross-sectional study, case study, observational study and case reports. Using this search strategy, 1231 citations were identified (See Table 2). These citations were cross-referenced with references provided from the manufacturer and public dockets and from bibliographies of published systematic reviews and meta-analyses; any additional titles were added for consideration.

Potentially suitable articles were requested via the FDA Biosciences Library. Practice guidelines were included if they were current and published by a professional or governmental organization charged with the oversight of a relevant aspect of psychiatric practice. Published systematic reviews and meta-analyses were included if they provided a comprehensive description of the search strategy and analysis.

Articles reporting primary data were included if ECT treatment was specified in the experimental protocol and the trial was a randomized, controlled design. This group of studies was evaluated

for scientific rigor and relevance by review team members using a ranking system that evaluated the study design, quality of study, clinical relevance, study size, measures used and statistical analyses conducted.

All studies were examined for safety and effectiveness outcomes. In terms of safety assessment, the most commonly studied adverse events were cognitive adverse events (including memory dysfunction). Some studies examined both effectiveness and safety measures; when appropriate, they were included in both analyses. Studies were included if they examined the following comparator groups:

- ECT vs. sham ECT
- ECT vs. placebo
- ECT vs. active medication
- ECT utilizing different waveforms (i.e., sine wave, brief pulse, ultrabrief pulse)
- ECT utilizing different electrode placement (i.e., bitemporal, bifrontal, unilateral dominant, unilateral non-dominant)
- ECT utilizing different energy dosages
- ECT with different frequency of treatment administration
- ECT + intervention to optimize safety/effectiveness vs. ECT without intervention
- Post-ECT course maintenance ECT (mECT) vs. continuation medication treatment

The effectiveness review included only RCTs employing standardized assessments of psychiatric symptomatology. Effectiveness studies generally examined depressive, manic or psychotic symptom outcomes. Many studies did not make a distinction between unipolar major depressive disorder MDD and bipolar depression. Since several studies noted comparable effectiveness of ECT for unipolar and bipolar depression (Bailine et al. 2010; Medda et al. 2009), a decision was made to review depressive illness (both unipolar and bipolar) together. Several RCTs were identified for mania and schizophrenia; no RCTs were found for catatonia (See Appendix 1: Effectiveness Studies). Studies that examined a mixed diagnostic population were included in analyses where subject populations were ≥ 50% of the total sample. Studies that examined subgroups of diagnostic populations (e.g., geriatric depression) were included in the analysis of the general diagnostic category. Meta-analyses were conducted for depressive illness and schizophrenia and studies were included if they used the Hamilton Depression Rating Scale (HDRS) or Brief Psychiatric Rating Scale (BPRS), respectively.

The cognitive adverse events systematic review included only RCTs employing standardized cognitive tests and acceptable statistical comparisons to: (1) assess subjects' cognitive status before and after ECT and/or (2) compare outcomes between subjects randomized to ECT treatment conditions differing in electrode placement, dosage, or waveform or comparing ECT to sham ECT. From the initial search strategy described above, of the 1231 citations returned, and cross-referencing the existing systematic reviews and meta-analyses, 122 potential studies were considered for inclusion (see Appendix 2: Cognitive Adverse Events Studies). Of those, 54 were excluded for various reasons (e.g., not actually randomized, no standardized instrument used, study design did not adhere to the comparison groups of interest). Sixty-eight (68) studies were examined in the systematic review of cognitive adverse events.

If papers were determined by clinical reviewers to meet criteria for inclusion into the systematic review and meta-analysis (respectively), data of interest was recorded on a spreadsheet database by the clinical reviewers. For the meta-analysis, in cases where an appropriate randomized comparison was conducted but insufficient data were reported, an attempt, when possible, was made to contact the authors. A total of seven authors were contacted, and four replied. In two cases, the supplemental information allowed for the inclusion of the study into the pertinent meta-analysis.

The review yielded the following number of studies for inclusion in this review:

Effectiveness

Systematic Reviews: 10
Meta-analyses: 7
RCTs: 76

Cognitive Adverse Events:

Systematic Reviews: 7
Meta-analyses: 4
RCTs: 68

In addition to cognitive adverse events, separate safety reviews were conducted to examine the association of ECT with neuropathological changes and death.

4. Safety Review

4.1 Public Docket Submissions

On September 10, 2009, FDA issued Federal Register Notice [Docket No. FDA-2009-N-0392] announcing the opening of a public docket to receive information and comments regarding the current classification efforts related to ECT devices. The docket closed on January 9, 2010 after receiving 3,045 responses. All responses were entered into a searchable database and were reviewed and coded according to certain key variables. The variables included:

- Respondent type
- Affiliate institution/organization
- U.S. or outside U.S.
- Use of form letter
- Number of individuals represented in comment
- ECT effect reported
- Position on reclassification
- Adverse event reported
- Supporting evidence provided
- Special population reported

The majority of respondents (59%) were members of the public not affiliated with an organization or the medical profession. Relatives or friends of ECT recipients constituted 12%

of respondents. Medical (including mental health) professionals constituted 11% of respondents (See Figure 1).

A majority of respondents, 79%, expressed an opinion against reclassification (i.e., maintain Class III designation) while 14% supported reclassification (i.e., reclassify to Class II). In addition, there were 92 group submissions, representing a total of 6462 individuals, against reclassification and 462 individuals in favor of reclassification.

A majority of respondents identified an adverse event they felt was associated with ECT treatment. The most common type of adverse event reported in the public docket was memory adverse event (529 reports). This was followed by other cognitive complaint (413 reports), brain damage (298 reports) and death (103 reports). Table 3 lists all adverse events reported in the public docket.

4.2 Manufacturer Docket Submissions

Two manufacturers responded to the April 9, 2009 Federal Register Notice [Docket No. FDA-2009-M-0101]), requesting information on the safety and effectiveness of their devices. Required contents of manufacturer submissions included: indications for use, device description, device labeling, risks, alternative practices and procedures, summary of preclinical and clinical data, and a bibliography. In addition, manufacturers were informed that they could also submit any information that would support reclassification into class I or II, including a formal reclassification petition, which should include: device identification, risks to health, recommendations, summary of reasons for recommendation (including special controls that would be sufficient to provide reasonable assurance of safety and effectiveness), and a summary of valid scientific evidence on which the recommendation is based.

The two manufacturers that currently market ECT devices in the U.S. responded to the request for information. Both manufacturers supported reclassification to Class II, and provided a summary of identified risks, as well as proposed mitigating factors (i.e., special controls). Reported potential risks included:

- Prolonged seizures
- Cardiac arrhythmias
- Complications of pre-existing medical conditions
- Death
- Brain damage (including structural injury, brain cell injury, hippocampal damage)
- Cognitive adverse events
    - Short-term confusion
    - Short-term memory loss
    - Long-term (persistent or permanent) memory loss
    - Risk of everyday or semantic memory loss
- Skin burns
- Electrical hazards (including risk of excessive dose administration)

Proposed mitigating factors (to be considered for special controls) included:

- Reducing the frequency of treatments during a course (i.e., increasing the time between treatments)
- Temporary or permanent interruption of treatments
- Reduction of stimulus dose (dose titration to determine minimal effective treatment levels)
- Electrode placement (i.e. right unilateral electrode placement)
- Dosage or type of anesthetic (or other) medications, including minimizing psychotropic medications
- Brief pulse or ultra-brief pulse waveform stimulus
- EEG monitoring to determine seizure length and quality, so that appropriate adjustments may be made for subsequent dosing levels

FDA comment: please note that the mitigating factors proposed by the manufacturers did not provide specific details regarding treatment parameters (e.g., specific stimulus dose, length of brief pulse, energy level, specific medications and dosages, etc.)

4.3 Manufacturer and User Facility Device Experience Database

The MAUDE database is maintained by the Office of Surveillance and Biometrics at FDA. This database contains adverse events and reportable product problems of medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. The reports are associated with all legally marketed devices. FDA has received 151 original adverse events reports (135 voluntary reports and 16 user facility reports) associated with ECT devices as of December 7, 2010. MAUDE reported adverse events are reported in Table 4.

As with the public docket submissions, the most commonly cited adverse event type was memory loss. In the MAUDE database, memory loss was reported in 117 cases, or 77% of all reports. General cognitive complaints (including learning disability) were mentioned in 30 cases (multiple complaints, e.g., both memory and cognitive adverse events, were mentioned in numerous reports). After memory and cognitive dysfunction, the most frequently reported adverse events included general emotional/psychiatric (i.e., increase in psychiatric symptoms), general motor (e.g., muscle weakness, tremor, gait abnormalities) and general functional disability (e.g., difficulties with activities of daily living or work). Of significance, brain damage was noted in nine cases, death was noted in two cases and suicide was noted in two cases (one reported a suicide attempt).

4.4 Identification of Significant Adverse Events

Combining information from all three sources, a comprehensive list of mentioned adverse events includes: memory dysfunction, general cognitive complaints, brain damage, death (including reports of reduced life span), onset/exacerbation of psychiatric symptoms, general motor dysfunction, general functional disability, headache, pain/muscle soreness, seizures (prolonged seizures), physical trauma, skin burns, neurological symptoms (e.g., paresthesias, dyskinesias),

respiratory complications/prolonged apnea, sleep disturbance, visual changes, nausea, hypertension, hypotension, cardiac complications, stroke, auditory complications, dental/oral trauma, suicidality, homicidality, substance abuse, urinary complaints, coma, and adverse reactions to anesthetic agents and neuromuscular blocking agents.

The most commonly cited complaint was memory dysfunction followed by other cognitive complaints. These two types of adverse events constituted the majority of adverse events reports of both the public docket and the MAUDE reports, and was mentioned in both manufacturer submissions. In addition, all three sources of information also mentioned the serious adverse events, brain damage and death.

Initial review of the results of the literature search for adverse events demonstrated a significant number of articles dealing with some aspect of memory and/or cognitive dysfunction, brain damage, or death. The largest number of articles (including RCTs) examined memory and cognitive dysfunction. A number of studies examined the issue of brain damage in ECT (mainly observational studies), and death (observational and epidemiological studies). The other mentioned adverse events were generally represented by a number of case reports or were not reported in the published literature.

Of note, the term "brain damage" appeared to have varying usages throughout all three sources of information. For the majority of the reports, the term "brain damage" was used without further elaboration of specific conditions or injury. When elaboration was provided, reports seemed to suggest a functional aspect of brain damage, such as problems with memory or cognition, or difficulty with everyday activities. Infrequently, the term was used to denote a structural anatomical brain lesion (e.g., "brain stem rupture" or "hippocampal damage") or neuropathological changes (e.g., "cell injury").

The identified risks, grouped according to affected system, are presented below.

1. Memory dysfunction
   Memory difficulties were mentioned in all three sources of information. In addition, numerous studies in the literature, including RCTs, have examined the issue of memory loss associated with ECT. This potential adverse event will be reviewed in detail in the next section.

2. General cognitive dysfunction
   General cognitive difficulties (in addition to memory loss) were mentioned in all three sources of information. In addition, numerous studies in the literature, including RCTs, have examined the issue of memory loss associated with ECT. This potential adverse event will be reviewed in detail in the next section.

3. Neuropathological changes
   Neuropathological changes were mentioned in all three sources of information. In addition, numerous studies in the literature, including RCT's and non-clinical basic research, have examined neuropathological changes associated with ECT. This potential adverse event will be reviewed in detail in the next section.

4. Death/reduced life span
   Death was mentioned as a potential adverse event in all three sources of information. Reduced life span was noted in the public docket responses. A number of observational and epidemiological studies have examined the rate of mortality associated with ECT. No reports or studies have examined reduced life span associated with ECT.

5. Onset/exacerbation of psychiatric symptoms (including manic switching)
   This category includes symptoms of depression, anxiety/fear/panic, hypomania/mania, mood lability, alterations in motivation and personality changes. Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects.

6. General motor dysfunction
   General motor dysfunction refers to complaints of muscle weakness or paralysis, prolonged tremor, and residual muscle twitching/spasms. Such complaints are not uncommon with ECT. Generally, symptoms are not severe and are time-limited.

7. General functional disability
   General function disability refers to reports of difficulties attending to activities of daily living, loss of normal functioning, difficulties with work or general decrease in quality of life. Differing degrees of functional loss have been reported. This appears to be a relatively common complaint associated with ECT which may result in significant effects on the experience of the patient.

8. Pain/discomfort
   Pain and somatic discomfort may manifest as headache, somatic pains, myalgias (muscle aches) or dizziness. Such complaints are relatively common with ECT. However, symptoms are not severe and are time-limited. Prolonged pain and discomfort may be treated with analgesic medication.

9. Prolonged seizures
   Prolonged seizures, including status epilepticus, though infrequent, have been reported with ECT. The occurrence of these adverse events is more likely in patients receiving medications that lower the seizure threshold, such as theophylline, or suffering from conditions that lower the seizure threshold, such as electrolyte imbalances or recent history of seizures. In order to mitigate this risk, pre-ECT evaluation typically includes a complete medical history, including neurological history, medication history, and review for conditions that may lower the seizure threshold. Medications may be adjusted or conditions that lower the seizure threshold may be treated prior to the initiation of ECT. Generally, the degree of risk is taken into account in determining whether ECT should be conducted, when it should be conducted, what precautions should be taken, and what clinical monitoring and management should take place. Electroencephalogram (EEG) monitoring should be available during and after the procedure to assess the induction and cessation of seizure activity.

10. Physical trauma
    In the past, physical trauma (e.g., fractures or soft tissue trauma) were not uncommon complications of ECT. However, with the use of general anesthesia and neuromuscular blockers, physical trauma is currently a rare event.

11. Skin burns
    Skin burns may result from ECT at the site where the electrode contacts the skin. In the past, complaints of burns were not uncommon, but appear to be less common currently. This may be because the energy delivered with new stimulation parameters is lower than in the past. Skin burns may be avoided with proper skin preparation, including the use of conductivity gel.

12. Neurological symptoms
    Various neurological symptoms have been associated with ECT treatment. These symptoms include paresthesias, speech difficulty, loss of coordination, and gait or balance disturbance. Such complaints are not uncommon with ECT. Generally, symptoms are not severe and are time-limited.

13. Pulmonary complications
    With cardiovascular complications, pulmonary complications are one of the most frequent causes of significant morbidity and mortality associated with ECT (APA 2001) The most common respiratory complications include prolonged apnea and aspiration. Prolonged apnea is a rare complication of ECT and generally occurs in patients who have a pseudocholinesterase deficiency and are slow metabolizers of succinylcholine, the most commonly used neuromuscular blocker (Packman et al. 1978). When this occurs, respiratory support (and general anesthesia) should be continued until the patient is able to breathe independently. If prolonged apnea occurs with succinylcholine, consideration may be given to using a lower dose, or using a nondepolarizing muscle blocker during the procedure. Aspiration is an uncommon but potentially severe complication associated risk of general anesthesia. Typical anesthesia procedures are employed to minimize the risk of aspiration.

14. Sleep disturbance
    Various disturbances in sleep have been reported with ECT treatment, including nightmares. These reports are rare, and no systematic studies have been conducted to examine this association.

15. Visual disturbance
    Changes in vision, visual impairment or corneal trauma (abrasion) are rare events that have been reported with ECT. Although rare case reports have been identified in the literature, no systematic studies have been conducted to examine this association. Corneal trauma is typically iatrogenic (caused inadvertently by a physician) in nature, and can be avoided if care is taken to avoid contact with the eyes during the procedure.

16. Nausea
    Nausea is a relatively common adverse event associated with ECT. It is generally not severe and is time-limited. Persistent nausea may be treated with medications.

17. Alterations in blood pressure
    It is well-established that an acute period of hypertension is typically associated with ECT treatment (Welch and Drop 1989). Generally, this period of hypertension is short-lived and blood pressure normalizes rapidly after the cessation of the seizure. Because hypertension is transient, it typically does not require treatment. However, if a patient has significant cardiovascular disease, medical management of blood pressure around the time of the treatment may be indicated. In order to mitigate cardiovascular risk, pre-ECT medical evaluation typically includes a complete cardiac history and examination with 12 lead EKG, and echocardiogram if clinically indicated. Hypotension occurs less frequently, and may occur as a result of significant cardiac disease, or may be iatrogenic (if antihypertensives were administered to manage the risk of hypertension). The degree of risk is taken into account in determining whether ECT should be conducted, when it should be conducted, what precautions should be taken, and what clinical monitoring and management should take place.

18. Cardiovascular complications
    Cardiovascular complications are one of the most frequent causes of significant morbidity and mortality associated with ECT (Welch and Drop 1989; Rice et al. 1994). The most common cardiovascular complications are cardiac arrhythmias and cardiac ischemia. Studies have demonstrated that ECT is associated with an increased rate of arrhythmias, especially in the post-treatment period (Huuhka et al. 2003). In order to mitigate cardiovascular risk, pre-ECT medical evaluation typically includes a complete cardiac history and examination with 12 lead EKG, and echocardiogram if clinically indicated. The degree of risk is taken into account in determining whether ECT should be conducted, when it should be conducted, what precautions should be taken, and what clinical monitoring and management should take place.

19. Stroke
    Rare reports of stroke have been made with ECT treatment. ECT is known to be associated with a significant increase in blood pressure during the acute phase of the treatment. Overall, the incidence of cerebrovascular complications with ECT is rare (Hsiao et al. 1987). While studies have suggested that patients with intracranial lesions may be at a slightly increased risk of stroke during ECT (Malek-Ahmadi and Sedler 1989), patients with cerebrovascular abnormalities, such as cerebral aneurysms or recent history of stroke may be at significantly increased risk of a hemorrhagic stroke (Wijeratne and Shome 1999; Krystal and Coffey 1997; Viguera et al. 1998). Small or chronic space-occupying lesions are thought to pose minimal increased risk. In order to mitigate this risk, pre-ECT medical evaluation typically includes a complete neurological history and examination. Neuroimaging may be considered if clinically indicated. The degree of risk is taken into account in determining whether ECT should be conducted, when it should be conducted, what precautions should be taken, and what clinical monitoring and management should take place.

20. Auditory complications
Rare reports of auditory symptoms have been reported with ECT treatment. These include decreased acuity, hyperacuity, and tinnitus. No systematic studies have been conducted to examine this association.

21. Dental/oral trauma
Given contraction of the jaw muscles during ECT due to direct electrical stimulation, significant teeth clenching typically occurs with ECT treatment. Cases of dental fractures or oral lacerations have been reported in response to the public docket and in the literature. In order to mitigate this risk, pre-ECT dental evaluation is typically conducted to assess the risk of damage, and mouth protection ("bite blocks") is placed in the patient's mouth prior to stimulation.

22. Suicidality
Increased suicidality has been examined by a number of published studies. These studies are generally observational in nature. Results of these studies have reported no increased suicidality associated with ECT treatment (Royal College of Psychiatrists [RCP] 2004). Non-randomized studies have suggested a decrease in suicidality with ECT (Bradvik & Berglund 2006; Kellner et al. 2005, O'Leary et al. 2001).

23. Homicidality
Rare reports of homicidality have been reported with ECT treatment. No case reports or studies have been published examining this association.

24. Substance abuse
Rare reports of increased use of illicit drugs have been reported with ECT treatment. Given the increased co-morbidity of psychiatric illness and substance abuse, it is difficult to determine the cause of increased substance use associated with ECT. No systematic studies have been conducted to examine this association.

25. Urinary complaints
Urinary symptoms such as urinary hesitancy, frequency or incontinence may be associated with ECT treatment. No systematic studies have been conducted to examine the association of urinary symptoms and ECT. Generally symptoms are not severe and are time-limited.

26. Coma
Rare reports of coma have been associated with ECT treatment. No systematic studies have been conducted to examine the association of coma and ECT.

27. Adverse reaction to anesthetic agents and neuromuscular blocking agents
All ECT in the U.S. is conducted with the application of modern anesthetic techniques, including induction with an intravenous (IV) anesthetic agent (such as propofol, methohexital or etomidate). In addition, to minimize the risk of physical trauma, including orthopedic fractures, a neuromuscular blocking agent is administered to the patient just

prior to the application of the ECT stimulus. Rare complaints of an adverse reaction to anesthetic agents and neuromuscular blocking agents have been reported. In the literature, the risk of these agents is low, though potentially severe (De Cosmo et al. 2005; Beamish and Brown 1981; Mertes and Laxenaire 2004).

A summary of these potential adverse events and their risks is presented in Table 5. The most frequently mentioned and extensively studied adverse events are:

1. Memory dysfunction
2. Cognitive dysfunction
3. Brain damage (i.e., neuropathological changes)
4. Death

These adverse events will be the focus of the literature review performed by FDA.

The Panel will be asked to consider whether memory dysfunction, cognitive dysfunction, brain damage (i.e., structural anatomical brain lesion or neuropathological changes) and death are the key risks associated with ECT that warrant further examination in determining a reasonable assurance of safety for ECT devices.

If not, what other adverse events warrant further examination?

4.5 Other Reported Concerns

Three other concerns (not related to a specific adverse event) were reported:

- Concern over improper consent procedures or forced treatment against a patient's wishes was noted in both the public docket and MAUDE database.
- Ineffectiveness of ECT for the primary psychiatric condition was mentioned in the MAUDE database.
- Device mechanical malfunction was reported in the MAUDE database as well, though the outcome for the patient in these cases was not specified.

4.6 Memory and Cognitive Adverse Events

A long-standing safety concern with the use of ECT is the potentially detrimental effect on memory and other cognitive function. Published studies have yielded mixed and confounding results. Part of this appears to be due to methodological issues (e.g., choice of cognitive test battery, timing of cognitive testing, etc.). In addition, the impact of depression itself on cognitive function influences cognitive test performance. The degree to which ECT ameliorates depressive symptoms can impact cognitive function. Furthermore, there is no systematic nomenclature regarding the various types of cognitive function. For example, studies of memory function include terms such as short-term memory, long-term memory, anterograde, retrograde, impersonal, personal, and autobiographical, among others. Moreover, because there are numerous, standardized cognitive tests available, studies have employed different test batteries, which make it difficult to conduct meta-analyses of cognition. Finally, more recent studies on the effect of ECT on memory and cognitive function have been limited by the lack of

randomized, double-blinded, sham-controlled trials, which are no longer considered ethical to conduct given the serious health impact in patients with refractory, treatment-resistant depression.

Given these limitations, FDA employed several methods to determine if scientific consensus exists regarding the effect of ECT on memory and cognitive function. These included:

- Examination of published practice guidelines
- Examination of published systematic reviews of cognitive function
- Examination of published meta-analyses of cognitive function
- FDA systematic review and meta-analyses of published RCTs investigating specific cognitive and memory domains

A full description of the FDA systematic review can be found in Appendix 1 and the FDA meta-analysis can be found in Appendix 2. A summary of both analyses is presented below.

4.6.1 Published Systematic Reviews, Meta-Analyses, and Practice Guidelines

a. A total of eight published review articles on the effect of ECT on cognitive function were identified: five systematic reviews (NICE 2003, Rose 2003, Fraser 2008, Gardner 2008, NICE 2009) and three meta-analyses (UK ECT Review Group 2003, Greenhalgh et al. 2005, Semkovska and McLoughlin 2010). Two practice guidelines were also identified (APA 2001, NICE 2003 and NICE 2009[update]).

   Generally these articles conclude:

   - There is clear evidence that memory and cognitive impairment (i.e., orientation, retrograde memory, anterograde memory and global cognitive function) occur both immediately after administration of ECT and following a course of therapy
   - The primary type of retrograde memory affected is autobiographical memory
   - Estimated "memory" loss ranges from 29% - 79% (Rose et al., 2003)
   - Sine wave stimulation is associated with a greater risk of memory and cognitive impairment than brief pulse stimulation
   - Bilateral (vs. unilateral) electrode placement and dominant (vs. nondominant) hemisphere placement is associated with a greater risk of memory and cognitive impairment
   - High energy dose ECT is associated with a greater risk of memory and cognitive impairment than low energy dose ECT
   - Raising electrical stimulus above the patient's seizure threshold was found to increase the effectiveness of unilateral ECT at the expense of increased memory and cognitive impairment
   - Limited evidence from controlled clinical trials suggests that the effects on memory and cognitive function may not last beyond 6 months
   - Subjective reports of memory loss may be more persistent (> 6 months post-ECT) than findings examining objective measures (up to 6 months) (Fraser 2008)
   - There is no evidence that ECT effect on memory and cognitive function differs among various other psychiatric diagnoses (e.g., mania, schizophrenia)

- It is likely that gains in ECT efficacy (via electrode placement and energy dosage adjustment) are achieved at the expense of increased risk of memory and cognitive side effects.
- There are individual differences on effects on cognition
- Memory and cognitive impairment may cause considerable distress to those affected
- Methodological issues such as lack of consistent definitions and use of non-standardized cognitive instruments hamper assessment of cognition.

More recently, Semkovska and McLoughlin (2010) conducted a systematic review and meta-analysis of objective cognitive performance associated with ECT. Their search strategy yielded a total of 84 studies consisting of nearly 3,000 unique subjects that met their criteria for inclusion in the meta-analysis. However, this study did not include any prospective, randomized controlled clinical trials, but did require that studies have pre- and post-ECT objective cognitive test data available for analysis. The main findings indicate that, in general, cognitive deficits are limited to the first 3 days post-ECT, which return and, possibly, improve to pre-treatment levels over time. Of note, while this study examined anterograde memory and other domains of cognitive and memory function, it did not examine retrograde autobiographical memory.

Semkovska and colleagues (in press) also conducted a meta-analysis of unilateral ECT effects on cognitive performance relative to: (1) bitemporal electrode placement, (2) electrical dosage, and (3) time interval between final treatment and cognitive reassessment. Thirty-nine studies (1415 patients) were included in the meta-analysis. The primary findings indicated that up to three days after final treatment, unilateral ECT was associated with significantly smaller decreases in global cognition, delayed verbal memory retrieval, and autobiographical memory, compared to bitemporal ECT. Higher electrical dosage predicted larger decreases in verbal learning, delayed verbal memory retrieval, visual recognition, and semantic memory retrieval. When retested more than three days after completing ECT, no significant differences remained between the two electrode placements; for unilateral ECT, electrical dosage no longer predicted cognitive performance whereas increasing interval between final treatment and retesting predicted growing improvement in some variables. This interval is a more useful long-term predictor of cognitive function than electrode placement or electrical dosage following unilateral ECT.

b. The two major practice guidelines that are published include the American Psychiatric Association (APA) task force on ECT and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom.

   Recommendations include:

   - Bilateral electrode placement is associated with a greater risk of cognitive impairment than unilateral electrode placement, and when unilateral electrode placement is utilized, high energy ECT dose is associated with a greater risk of cognitive impairment than low energy dose ECT (NICE 2009).

- During a course of ECT, the presence and severity of disorientation, anterograde amnesia, and retrograde amnesia should be monitored in terms of both objective findings and self-report. This evaluation should consist of bedside assessment of orientation and memory (both retention of newly learned material and recall of recent and remote events) and/or administration of formal neuropsychologic measures (APA 2001).
- Assessment should be carried out before ECT and at least weekly throughout an ECT course. When possible, cognitive assessment should be performed at least 24 hours after an ECT treatment (APA 2001).
- If orientation and/or memory deteriorate substantially during an ECT course, modifications to the ECT procedure should be considered. If such effects persist after completion of the ECT course, a plan should be made for post-ECT follow-up assessment (APA 2001).
- Physicians administering ECT should review the potential contribution of concomitant medications, ECT technique and spacing of treatments, and then take appropriate action (APA 2001).

The ECT task force of the APA is currently updating its practice guidelines and will be publishing this update in the near future.

4.6.2 FDA Systematic Review and Meta-Analysis of Cognitive Literature

a. Methodology

Cognitive domains for review were established by the review team. Classification of cognitive domains is not mutually exclusive as there is considerable overlap among various cognitive functions and robust intercorrelations among specific domains. By convention, the practice of clinical neuropsychology characterizes cognitive function into the following categories:

- Global cognitive function – often used in the screening of general mental status usually by a non-neuropsychologist at the bedside (e.g., Mini-Mental State Examination [MMSE]).
- Orientation - awareness of self in relation to one's surrounding (e.g., identification of person, place, and time). For ECT, time to re-orientation following treatment is commonly studied.
- Executive function – capacity to attend to, plan, organize and execute a behavioral response, including but not limited to:
    - Attention/concentration,
    - Mental tracking, planning, organization and execution of motor/behavioral response,
    - Problem-solving, judgement and reasoning,
    - Response inhibition,
    - Set-shifting,
    - Working memory (capacity to hold information in short term storage in order to execute a cognitive response).

- Memory function – including capacity to recall previously learned (and stored) information, both personal and impersonal and the ability to encode, store and recall (recognize) novel information. Assessment of memory must include both verbal and non-verbal information. Review of the ECT literature on mnemonic function includes the following terminology:
    - Global Memory Function – typically a comprehensive battery of tests assessing attention/concentration, retrograde (impersonal) memory, and various verbal and non-verbal anterograde memory task (e.g., Wechsler Memory Scale [WMS]),
    - Anterograde Memory – capacity to encode, store and retrieve novel information verbally and non-verbally after a course of ECT therapy (typically includes assessment of both free delayed recall and cued recognition),
    - Retrograde Memory – capacity to retrieve information encoded *prior* to initiation of ECT therapy:
        - Personal (autobiographical) memory – typically reported as a percent recall of baseline-established past personal information and events
        - Impersonal memory – capacity to recall historical or factual information (e.g., past presidents, direction of sunset, etc.)
    - Subjective Memory – typically a patient self-report inventory of perceived memory problems following a course of ECT treatment
- Language function – capacity to express and comprehend linguistic material and often includes assessment of fluency, naming, comprehension, reading, writing and arithmetic calculations,
- Visuospatial function – capacity to understand and carry out activities dependent upon intact spatial abilities, including visuomotor, visuoconstructive, and perceptual (motor-free) tasks,
- Praxis/Gnosia – capacity to carry out previously learned activities (e.g., buttoning a shirt)/the perceptive faculty enabling one to recognize the form and the nature of persons and things.

The most commonly used measure to assess retrograde personal memory is the autobiographical memory interview (AMI). The AMI (and the AMI short form, AMI-SF) was developed to standardize the collection of autobiographical data and to provide a range of time spans and item types (Kopelman et al, 1989). It contains two sections: an autobiographical incidents schedule and a personal semantic memory schedule from three time blocks: childhood, early adult life, and recent events. Initial validation of the AMI correlated the questionnaire scores with other remote memory tests, producing coefficients in the 0.27 - 0.76 range with most at or above 0.40 correlation. Amnestic patients performed significantly below control subjects on all variables, with the greatest difference between these groups occurring on the recent events memory score. Overall, this technique appears to satisfy practical requirements as a test of retrograde (remote) memory (Lezak, 1995).

There are no published prospective RCTs without crossover between treatment groups that examined cognitive outcomes at more than six months after ECT. In addition, the type and severity of cognitive adverse events likely differ in relation to the time elapsed following a course of ECT. Therefore, for each of the above categories of cognitive function, available data on cognitive effects were categorized into five time points following ECT treatment:

- Immediately post-ECT: acute effects within 24 hours of ECT seizure termination,
- Subacute effects: greater than 24 hours to less than two weeks after receiving a course of ECT,
- Medium-term effects: two weeks to less than three months after receiving a course of ECT,
- Longer-term effects: three months to less than six months after receiving a course ECT,
- Long term effects: six months or greater after ECT.

b. Systematic Review and Meta-analysis by Cognitive Domain

A more detailed account of the systematic review and meta-analyses conducted by FDA is found in Appendices 1 and 2, respectively. A list of RCTs considered for the systematic review and meta-analysis can be found in Table 6. Given the lack of RCTs utilizing the appropriate standardized scale, the appropriate comparison groups within a comparable timeframe, and sufficient reporting of results, meta-analyses were conducted only in three cognitive domains: time to reorientation, global cognition (MMSE), and retrograde autobiographical memory (AMI). These meta-analyses, utilized the results of two to four studies. In addition, a meta-analysis was conducted of non-randomized data (reported within RCTs) comparing the change in AMI between pre-treatment and post-treatment (Figures 2-5).

Conclusions of these analyses are provided by cognitive domain below.

i. Time to reorientation

There are sufficient data to conclude that bilateral ECT is associated with longer disorientation than right unilateral, left unilateral, or unilateral non-dominant electrode placement. While relatively weaker, there is evidence to suggest that bifrontal ECT is associated with longer periods of disorientation than bitemporal ECT (and high dose ECT is associated with longer disorientation than low or moderate dose ECT). There is no evidence that disorientation following ECT is long-term or persistent.

The meta-analysis (Figures 6-10) demonstrates that electrode placement significantly affected time to reorientation (bilateral more than unilateral), increasing it by 18 seconds (unilateral medium vs. bilateral low) to 29 seconds (unilateral low vs. bilateral high). Patients receiving bilateral ECT at high doses had on average a 29-second longer time to reorientation compared to those

patients receiving unilateral ECT at low doses. However, the effect of energy level seemed less relevant than electrode placement. Patients receiving unilateral ECT at low energy compared to those receiving unilateral ECT at medium energy had on average a time to reorientation that was seven seconds longer, while there was no statistically significant difference between bilateral low to bilateral high energy levels.

ii. Executive function

Immediately following ECT, most data suggest that there is no significant change from baseline in executive function. There is no conclusive evidence that bilateral ECT is associated with greater executive dysfunction than unilateral ECT. No differences were found between bifrontal and bitemporal ECT. Brief pulse ECT showed greater acute executive dysfunction than ultrabrief pulse in one study. There is no statistically significant decline in executive function from baseline in patients receiving a course of ECT therapy and executive function may actually improve (possibly due to treatment of the underlying disorder).

For sub-acute effects of ECT, there is conclusive evidence that executive function following bilateral ECT is not worse than unilateral ECT and there is no significant change from baseline in this time period. There is limited evidence that sine wave stimulation is not significantly different from pulse wave and high energy is not significantly different from low energy. One study suggests that left unilateral ECT may be associated with greater executive dysfunction than right unilateral.

For medium term effects, there is conclusive evidence suggesting no significant change from baseline in executive function. There is limited evidence of no difference in executive function between bilateral and unilateral ECT. Findings are conflicting regarding ECT vs. sham, waveform (sine vs. brief pulse) and variations in energy dose.

There is limited long-term data on executive function. Therefore, no meaningful conclusions can be drawn.

iii. Global Cognitive Function

Immediately post-ECT, there is limited evidence to suggest that bilateral ECT is significantly worse than unilateral ECT. There is no clear consensus as to change in global cognitive function from baseline.

Sub-acutely, there is limited evidence that bitemporal ECT is worse than bifrontal ECT. The results are equivocal regarding electrode placement, energy dose differences and change from baseline in global cognitive function.

In the medium term, there are no differences in global cognitive function between ultrabrief pulse bifrontal compared to ultrabrief pulse unilateral ECT; both modalities are associated with improvement from baseline at six weeks.

For longer-term effects, there is evidence to suggest improvement or no change in global cognitive function from baseline.

The meta-analysis (Figures 11-18) demonstrated that immediately post-ECT, bilateral ECT was associated with 6-10% worse MMSE scores than unilateral placement. There was no statistically significant difference in unilateral electrode placement with low energy compared to medium energy or in bilateral electrode placement comparing low energy to high energy. This disparity continued (and increased) at two months post-ECT. Patients receiving bilateral high dose ECT had on average 12% worse performance on MMSE compared to those receiving unilateral low dose ECT.

iv. Global Memory

There are limited data regarding change in global memory function immediately following treatment.

For the sub-acute period, there were no significant differences between unilateral and bilateral electrode placement, or high and low dose energy dosage. The results are equivocal regarding change from baseline.

For the medium term, there is limited evidence that bilateral ECT three times per week is associated with significantly worse global memory loss than two times per week. There is limited evidence that there is no significant change from baseline. No data exist on differences in electrode placement, waveform (sine vs. brief pulse or energy dose.

At six months, there are limited data that there is no significant difference in global memory between ECT and sham, and change from baseline to six months.

v. Anterograde Verbal

The findings regarding verbal anterograde memory impairment suggest the following:

- Equivocal findings regarding verbal anterograde memory impairment in studies comparing the effect of ECT vs. sham ECT,
- Bilateral electrode placement and left unilateral electrode placement appear to be associated with greater anterograde verbal memory impairment,
- The literature suggests that sine wave vs. brief pulse ECT is associated with greater anterograde verbal memory impairment,

- About 1 week after ECT therapy, verbal memory function following right unilateral electrode placement and low/moderate energy dose ECT may return to baseline and might improve,
- About 2 weeks after ECT therapy, verbal memory function following bilateral electrode placement may return to baseline and studies suggest that verbal memory might improve,
- At 6 months post-ECT, there are limited data to suggest that no differences are present between ECT and sham ECT or bilateral vs. unilateral nondominant hemisphere electrode placement, and there is no change or improvement compared with baseline.

vi. Anterograde Non-verbal

Immediately post-ECT, there are data that ECT is associated with more decline than sham ECT. There are no differences with respect to electrode placement. Brief pulse may be worse than ultrabrief pulse. There does not appear to be any change from baseline.

Subacutely, no differences are noted among any of the ECT treatment parameters. There are equivocal findings regarding detectable changes from baseline.

After two weeks post-ECT, there is no conclusive evidence to support any differences among the ECT treatment parameters with regard to decline. There is conclusive evidence that there is no change from baseline.

vii. Retrograde Impersonal Memory

Immediately following ECT, the data appear equivocal. In one study comparing ECT and sham, the data suggest poorer retrograde impersonal memory with sham treatment compared to ECT. However, retrograde memory improved after eight hours following treatment in both groups. There is some evidence to suggest that electrode placement is a factor, with bilateral placement resulting in poorer performance compared to unilateral placement. There is equivocal evidence regarding change from baseline.

Subacutely, there is equivocal evidence to suggest impairment with respect to electrode placement, pulse or energy dose. There is also conflicting evidence regarding detectable changes from baseline performance.

For the medium term, there are equivocal findings among the ECT treatment parameters. In a single study, the bilateral (not unilateral) group improved significantly from baseline.

There are no studies reporting retrograde impersonal memory data from three to less than six months following ECT.

At six months, no differences are seen between ECT and sham ECT, electrode placement or pulse wave. The data do not demonstrate a significant change at six months compared with baseline.

viii. Retrograde Personal (Autobiographical) Memory

Immediately after ECT, there is limited evidence to suggest that bilateral electrode placement is associated with greater impairment. There is limited evidence that ECT is associated with a decline in autobiographical memory immediately post-ECT (compared with baseline).

Subacutely, there is conclusive evidence to support the finding that bilateral ECT is associated with greater retrograde personal memory impairment compared with unilateral, right unilateral or unilateral non-dominant ECT samples. There is limited evidence with respect to sine wave worse than brief pulse and high energy dose worse than low. There is evidence to suggest a decline from baseline with ECT (except for ultrabrief pulse stimulus that did not demonstrate a significant change from baseline). One study of ultrabrief pulse unilateral and bifrontal ECT showed improvement in retrograde personal memory compared to baseline at one and six weeks.

For the medium term (2 weeks to <3 months), there are limited data regarding the effects of electrode placement, pulse or energy dose, although the studies reviewed appear to suggest no significant differences in test performance with respect to these treatment parameters. In addition, there are limited data with respect to change from baseline, although studies suggest no change in retrograde personal memory, or improvement (with ultrabrief pulse waveform).

At three months, data are limited (two studies) and yield conflicting results. One study (Weiner 1986; n=74) demonstrates that bilateral ECT is worse than unilateral non dominant and sine wave is worse than controls, with a trend for subjects receiving sine wave stimulus performing worse than those receiving brief pulse. Another study (Smith 2010; n=85) examined three and six month data but compared these scores with post-ECT course baseline scores. They found that bilateral continuation ECT after an acute course of ECT is associated with worse autobiographical memory performance compared to continuation drug treatment at three months. It is important to note that this difference was due to significant improvement over post-ECT baseline in the continuation drug therapy group compared with no change in the continuation ECT group at three months.

At the six-month time period, only one study (Weiner 1986; n=74) examines autobiographical memory, comparing pre-ECT course scores with post-ECT course scores. In this study, scores have improved since the three-month time period, with brief pulse unilateral treatment demonstrating a decline from baseline, but similar to those of normal controls (non-randomized subjects who did not receive ECT).

Because of the importance of ECT effect on autobiographical memory, additional analyses were run. In RCT's that reported pre-ECT and post-ECT scores for autobiographical memory scales, pre-treatment baseline scores were compared with follow-up scores. It is important to note that these comparisons were purely observational as this analysis amounted to change scores within subjects. In addition, to expand the database, two additional measures of autobiographical memory (both of which had been compared against the AMI) were considered: the personal and impersonal memory test-personal section (PIMT-P) (Lisanby 2000), the Duke personal questionnaire (McCall 2000), and the personal memory questionnaire (PMQ) (McCall 2000).

In terms of change from baseline, ten studies examining autobiographical memory using the AMI, PIMT (validated against the AMI), PMQ or Duke personal memory questionnaire report % recall (or % amnesia) when comparing pre-ECT and post-ECT performance. These studies are summarized in Table 7. An examination of these non-randomized, within subjects, pre-ECT to post-ECT comparisons demonstrates acute recall rates (within one week) of 70-90% with moderate to high dose right unilateral treatment, and 50-60% with high dose right unilateral treatment. Bilateral treatment is associated with 40-70% recall within one week after ECT. Ultrabrief pulse stimulus (regardless of electrode placement) demonstrates 94% recall in the acute period. Finally, data from two to six months post treatment demonstrates recall rates 5-10% better than in the acute phase, and about 70% at two months and about 80-90% (for non-sine wave stimulus) at six months.

In addition, a meta-analysis was performed using data from five of these studies. At one day to one week post-treatment, percent change scores from pre-ECT baseline to follow-up were approximately 74% for right unilateral ECT (at low or moderate energy dose), and 58-66% for bilateral ECT (at low or moderate energy dose). These meta-analyses are presented in Figures 19-23.

ix. Subjective Memory.

There are several methodological issues with regard to the use of self-reported, subjective complaints of memory impairment. Most notably, subjective memory assessment relies heavily on the use of self-report scales and appear highly dependent upon the time these scales are completed. Furthermore, subjective reports of memory impairment may be associated with the degree to which depressive symptoms resolve (Abrams, 2000). In general, patients are more likely to report memory impairment immediately following ECT treatment.

There are no randomized trials of subjective memory within the first 24 hours of administration of ECT.

Subacutely, there are sufficient data to conclude that bilateral ECT is associated with more subjective memory complaints than unilateral ECT. In terms of change from baseline, there is strong evidence to suggest that subjective memory improves after a course of ECT.

There is only one study with data for the medium term which reports no difference between unilateral and bilateral ECT at one month.

There are limited data on subjective memory function at six months. Overall, there appears to be no difference in subjective memory assessment between ECT and sham, or any of the ECT treatment factors. There is some evidence showing improvement or no change in subjective memory compared to baseline.

x. Cognitive Adverse Events – Summary

The FDA review of the literature suggests the following conclusions:

Acute cognitive impairment associated with ECT includes transient disorientation, which appears longer in bilateral than in unilateral ECT. However, there is no evidence that disorientation following ECT is long term or persistent.

The literature suggests that there is no statistically significant decline in executive function from baseline in patients receiving a course of ECT therapy and that executive function may actually improve.

There is no clear consensus as to change in global cognitive function (e.g., as measured by the MMSE) from baseline acutely or subacutely, but there is limited evidence suggesting an improvement or no change from baseline at three to less than six months.

The initial decreases in verbal and non-verbal anterograde memory return to baseline, and verbal anterograde memory might continue to improve after two weeks post-treatment. Bilateral or left unilateral electrode placement, as well as sine wave ECT, appear to be associated with greater anterograde verbal memory impairment. There is some data to suggest that no differences in anterograde memory are present between ECT and sham ECT or between bilateral and unilateral nondominant ECT by six months.

There is some evidence to suggest that there may be some decline from baseline in retrograde impersonal memory subacutely, although not with ultrabrief pulse. While bilateral ECT was shown to be worse than unilateral ECT in effects on retrograde impersonal memory subacutely, there is no difference by electrode placement and no change from baseline by six months.

In the first two weeks after standard ECT, there appears to be a decline from baseline in retrograde personal (autobiographical) memory; ultrabrief pulse and

bifrontal ECT conversely, may result in improvement. Studies conclusively support the finding that bilateral ECT is associated with greater autobiographical memory impairment compared with unilateral, right unilateral or unilateral non-dominant ECT samples, but these differences and the change from baseline are less consistently noted by two weeks to less than three months, with possible improvement in ultrabrief pulse ECT. At three to six months, data are limited and inconsistent.

The literature notes methodological issues with regard to the use of self-reported, subjective complaints of memory impairment. There is strong evidence that subjective memory reports demonstrate improvement from baseline after a course of ECT. However, subjective impressions of improvement in memory after a course of ECT may be associated with improvement in depressive symptoms. There is sufficient data to conclude that bilateral ECT is associated with more subjective memory complaints than unilateral ECT in the first two weeks only. At six months, there are limited data demonstrating no difference in subjective memory assessment between ECT and sham; continuation ECT and continuation medication; sine and pulse wave stimulus; and bilateral and unilateral electrode placement.

The Panel will be asked to consider if there is sufficient evidence to support a claim of reasonable assurance of safety with regard to:

a) anterograde memory functioning (verbal and non-verbal), and
b) retrograde functioning (impersonal and autobiographical) memory.

In addition, are there any other cognitive or memory risks that were not examined that may present a significant safety risk associated with ECT? If so, what are they?

4.7 Neuropathological Changes

A separate search was conducted to review the literature regarding neuropathological changes associated with ECT. This search via PubMed for all studies published through July 1, 2010. Search terms were included as both text and MESH headings and included the following: "electroconvulsive therapy," "electroshock," "electroconvulsive shock," "brain/pathology," "brain injuries," "brain damage," "tissue damage," "adverse effects," and "nervous system." Studies were limited to "human," "animal" and "English." This initial search strategy produced 1008 citations which were systematically sorted. Studies were evaluated for scientific rigor by a neuroscientist and were sorted based on the species used in the study, brain regions analyzed, and the type of neuropathology found. Studies that mentioned the use of electroshock that was not electroconvulsive in nature were removed. Studies that addressed adverse effects due to electroshock that did not focus specifically on brain morphology were also removed. Using these criteria, 84 potential studies were identified and examined in the review of neuropathological changes (i.e., "brain damage").

Direct and Indirect Potential for Damage

Because the brain is the target 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 is most likely to occur from temperature elevation from heat liberated by the electrical stimulation or from cerebral anoxia (i.e., reduced level of oxygen) 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 et al., 1976). Considering the worst-case (i.e., smallest volume) calculation that assumes 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 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 is greatly reduced by the aforementioned shunting through the scalp. Also, because ECT has, for more than 50 years, been administered concurrently with full oxygenation of the patient to consistently yield a partial oxygen pressure of at least 100 mm Hg (Posner et al., 1969), cerebral anoxia has been essentially eliminated as a possible cause of any putative brain injury during ECT.

There is a growing body of literature examining changes in brain morphology after induced seizures. Brain injury by indirect means from ECT-induced seizures is an obvious safety concern, and recent research has aimed to understand both the gross and microscopic changes that occur in the brain due to ECT. Additionally, researchers have hoped to garner a better understanding of the potential mechanism(s) that underlie this treatment. Both animal and human studies have aimed to elucidate the biological response in the brain, at the gross pathologic and molecular levels.

Autopsy and neuroimaging data

While most animal studies have focused on a rodent model, there are also recent non-human primate studies of the effects of electroconvulsive shock (ECS), which is the animal model of ECT. Two papers by Dwork et al. (2004; 2009) demonstrate that ECS, at a dose comparable to human treatment, does not produce histological lesions nor does it lead to a change in number of neurons or glia (non-neuronal brain cells) in vulnerable regions of the brain. These data are further supported by Magnetic Resonance Imaging (MRI) studies that demonstrate no structural changes in the brain after ECT treatment (Coffey et al. 1991; Ende et al., 2000). Recent MRI studies also suggest a neuroproliferative role for ECT as researchers have witnessed an increase in hippocampal volume and frontal white matter in human patients post-treatment (Nordanskog et al., 2010; Nobuhara et al., 2004).

Immunohistochemical data

Similar neuroproliferative results have been demonstrated in immunohistochemical studies of the brain pre- and post-ECS treatments. In a study by Perera et al. (2007), no cell death was noted in

the brains of monkeys post-ECS treatment. The authors instead witnessed an increase in precursor cell proliferation in the hippocampus (Perera et al., 2007). Similar findings in mouse studies have been published in recent years. In many instances, researchers have recorded neurogenesis and synaptogenesis in the brain (i.e., the hippocampus) of rats treated with ECS (Vaidya et al., 1999; Malberg et al., 2000; Madsen et al., 2000; Hellsten et al., 2004; Chen et al., 2009). Conversely, a handful of studies also show that ECS in rodents may lead to synapse loss and neuronal cell death (Lukoyanov et al., 2004; Zarubenko et al., 2005; Cardoso et al., 2008). While these studies may underlie some of the mechanisms of ECT, the indirect effect it has on the brain is not well understood.

Biomarkers for damage

After brain injury in humans, there are detectable increases in a variety of molecules in blood and/or cerebrospinal fluid (CSF). These molecular entities can be measured before and after ECT in an attempt to determine whether ECT leads to damage. In blood serum, concentrations of brain-cell damage markers such as C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) all remained within a normal range in patients tested before and after ECT treatments (Giltay et al., 2008). Similarly, when measuring neuron-specific enolase (NSE), a marker of neuronal damage in blood serum, there was no difference in NSE levels before and after treatment with ECT (Berrouschot et al., 1997; Agelink et al., 2001; Palmio et al., 2010). Finally, in a study that measured CSF biomarkers, levels of CSF-tau, CSF-NFL and CSF-S-100 beta protein, all markers of neuronal glial degeneration, and the CSF/S albumin ratio, a measurement of potential blood brain barrier (BBB) dysfunction, were not significantly changed by a therapeutic course of ECT (Zachrisson et al., 2000). A recent paper shows evidence of a transient increase in blood serum S-100 levels in 4 of the 10 patients treated with ECT (Palmio et al., 2010). No significant increase in NSE levels was detected in those 4 patients nor were there any significant changes in NSE or S-100 levels in the 14 patients studied in the Agelink study (2001). These studies provide some evidence that ECT does not lead to a brain inflammatory response, brain cell leakage, neuronal damage or BBB dysfunction.

The Panel will be asked to consider, while the manufacturer and public dockets both indicated "brain damage" as a potential risk associated with ECT, the FDA review of the literature identified no evidence of gross anatomical/histological, immunohistochemical, or biomarker of injury evidence to support this association. Is there sufficient evidence to support a claim of reasonable assurance of safety with regard to neuropathological changes?

4.8 Death

Estimates of the mortality rate associated with ECT treatment are 1 per 10,000 patients or 1 per 80,000 treatments (APA 2001; Watts et al. 2010). This rate is estimated to be approximately the same as the rate associated with minor surgery (APA 2001; Badrinath et al. 1995; NICE 2003). An examination of ECT use in California from 1977-1982 demonstrated that approximately 1.12 persons per 10,000 population received ECT. The mortality rate was 0.2 deaths per 10,000 treatments (Kramer 1985). In a follow-up to this study, ECT use in California was examined from 1984-1994. During this time a total of 28,437 patients received 160,847 treatments. Three

deaths were reported, which resulted in a rate of 0.19 deaths per 10,000 treatments (Kramer 1999).

Nuttall and colleagues (2004) conducted a large retrospective review of ECT. They examined 2,279 patients who underwent 17,394 ECT treatments. Twenty-one patients (0.92%) experienced a complication during their series of ECT (median number of treatments = 7). Cardiac arrhythmias represented the majority of complications. Although there were no occurrences of permanent injury or death immediately after ECT, there were 18 deaths within 30 days of the last treatment, but none were thought to be related to ECT. It is reported that death rates have been declining in recent years (possibly due to improved monitoring and medical management during ECT treatment).

The Panel will be asked to consider: is there sufficient evidence with regard to the mortality rate associated with ECT given current administration techniques to support a claim of reasonable assurance of safety for ECT devices?

5. Effectiveness Review

5.1 Published Systematic Reviews, Meta-Analyses, and Practice Guidelines

1. A total of 17 published review articles examining the effectiveness of ECT for psychiatric indications were identified, including ten systematic reviews (Witerajne 1999, NICE 2003, van der Wurff 2003, Guillen 2004, Valenti 2008, Ross 2006, Rasmussen 2009, Stek (Cochrane Review) 2009, NICE 2009, Jager 2010) and seven meta-analyses (Janicak 1991, Kho 2003, UK ECT Group 2003, Pagnin 2004, Greenhalgh 2005, Parker 1992, Tharyan (Cochrane Review) 2002). Three practice guidelines were also identified (APA 2001, RCP 2004, NICE 2003/2009).

    a. For depressive illness, these articles generally conclude:
        - Evidence for the effectiveness of ECT exists only for acute effects (immediately post-ECT course to one month),
        - ECT is probably more effective than sham or placebo,
        - The overall treatment effect of ECT has been estimated to be 78%,
        - The presence of psychotic symptoms may predict better response,
        - Bilateral ECT is probably more effective than unilateral,
        - Increased electrical stimulus above seizure threshold (ST) increases efficacy of unilateral ECT at the expense of increased memory and cognitive impairment,
        - Unilateral ECT with an energy dosage at or just above seizure threshold may be no more effective than sham,
        - Unilateral ECT with an energy dosage > 150% seizure threshold may be at least as effective as bilateral ECT with an energy dosage at or just above seizure threshold,
        - ECT is probably more effective than some antidepressants,
        - ECT plus medication is not superior to ECT alone in the short-term,

- Compared with placebo, continuation pharmacotherapy with tricyclics or lithium reduced the rate of relapse post-ECT response,
- There is limited evidence that ECT is more effective than repetitive transcranial magnetic stimulation,
- There is limited evidence to support the effectiveness of ECT for elderly patients (van der Wurff 2003; Stek 2009),
- Little evidence exists supporting the long-term effectiveness of ECT,
- Tricyclic (TCA) medication administration may improve the antidepressant effect of ECT during course of treatment,
- Continuation TCA with lithium decreases relapse,
- Gains in efficacy are achieved only at the expense of increased risk of cognitive side effects,
- There is no evidence to suggest that the mortality associated with ECT is greater than that associated with minor procedures involving general anesthetics,
- There is no evidence to suggest that ECT causes brain damage.

Two of the systematic reviews question the effectiveness of ECT for treating depression. One article noted that there was no evidence of a significant difference between real and sham ECT at one month post-treatment (Ross 2006). Another questioned the finding of a significant difference between and sham ECT, pointing to high sham response rates and differential response to depressive subtypes (Rasmussen 2009).

b. Schizophrenia

- Evidence for the effectiveness of ECT for schizophrenia exists only for acute effects; there is no evidence of effectiveness beyond the acute phase,
- There is conflicting evidence that ECT may be more effective than antipsychotic medication for acute episode (for certain types),
- There is limited evidence that ECT may reduce relapses,
- ECT probably results in a greater likelihood of being discharged from hospital,
- There is no evidence that ECT demonstrates effectiveness in other than the acute setting.

c. Bipolar Mania

- There is limited evidence that ECT may be effective in treating mania.

d. Bipolar Mixed States

- There is limited evidence that ECT may be an effective, and potentially underutilized treatment of mixed states (Valenti 2008).

e. Schizoaffective Disorder

- There is no evidence that ECT is effective for schizoaffective disorder at any time point (Jager 2010).

2. Practice Guidelines

Three major practice guidelines have been published on ECT. These guidelines include:

- APA Task Force on ECT (2001)
- Third report of the Royal College of Psychiatrists' Special Committee on ECT (2004)
- National Institute for Health and Clinical Excellence (NICE 2003; NICE 2009)

There is significant agreement between the three sets of recommendations. The following outlines the combined recommendations of the three major practice guidelines.

Treatment recommendations regarding principal diagnostic indications of ECT:

- Severe depression (unipolar and bipolar)
- Acute mania (and bipolar mixed states)
- Schizophrenia
- Catatonia

ECT should be considered for primary use (i.e., prior to medications) in the following situations):

- A need for rapid, definitive response because of the severity of a psychiatric or medical condition (e.g., when illness is characterized by stupor, marked psychomotor retardation, depressive delusions or hallucinations, or life–threatening physical exhaustion associated with mania)
- When the risks of other treatments outweigh the risks of ECT
- A history of poor medication response or good ECT response in one or more previous episodes of illness
- The patient's preference

ECT should be considered for secondary use (i.e., after one or more medication trials) in the following situations:

- Treatment resistance to antidepressant medications
    - For depression, after one or more antidepressant trials
    - For mania, after one or more mood stabilizer trials with adjunctive atypical antipsychotic treatment
    - For clozapine resistant schizophrenia
    - For lorazepam resistant catatonia
- Intolerance to or adverse effects with pharmacotherapy that are deemed less likely or less severe with ECT
- Deterioration of the patient's psychiatric or medical condition creating a need for a rapid, definitive response.

If response or remission has been achieved with ECT, antidepressants (including lithium augmentation) should be started or continued to prevent relapse.

ECT should not be recommended for an individual with moderate depression or who has not responded well to a previous course of ECT.

3. Individuals considering ECT should be fully informed of the risks associated with ECT, and with the risks and benefits specific to their individual situation, including consideration of the risks associated with a general anesthetic, current medical comorbidities, potential adverse events (notably cognitive impairment) and the risks associated with not receiving ECT. This discussion should be documented and a valid informed consent should be signed and obtained.

5.2 FDA Systematic Review and Meta-Analysis of Effectiveness RCT's

1. Methodology

FDA conducted its own systematic review and meta-analysis of the published RCT's examining the effectiveness of ECT. Study designs considered for the indication of depression included:

- ECT vs. Sham (Table 8)
- ECT vs. Placebo(Table 9)
- ECT vs. Antidepressant medications (Table 10)
- Comparisons of different waveforms (sine wave, brief pulse, ultrabrief pulse)
- Comparisons of different electrode placements (bilateral, unilateral) (Table 11)
- Comparisons of different energy dosages (low = at or just above seizure threshold, moderate = 1.5 – 3 times seizure threshold, high > 3 times seizure threshold) (Table 11)
- Comparisons of different administration schedules (two times per week, three times per week) (Table 12)

In addition, ECT studies for schizophrenia (Table 13) and acute mania (Table 14) were also examined. No RCTs were identified for catatonia, schizoaffective or schizophreniform disorder.

Following the methodology described, potential studies for specific comparisons were identified. These are listed below by study design:

- Depression: ECT vs. Sham: 11 RCTs
- Depression: ECT vs. Placebo: 6 RCTs
- Depression: ECT vs. Antidepressants: 18 RCTs
- Depression: Electrode placement and Energy Dosage: 22 RCTs
- Depression: Frequency: 2 vs. 3 times per week: 6 RCTs
- Schizophrenia: ECT vs. Sham: 10 RCTs
- Mania: ECT vs. Sham: 6 RCTs

2. Results

A summary of conclusions for the systematic review and meta-analysis for each comparator analysis is presented below. A detailed description of the systematic review and meta-analysis for effectiveness is presented in Appendices 3 and 4, respectively. A summary of both analyses is presented below

a. ECT vs. Sham for Depression

In terms of immediate post-ECT effects, there is sufficient evidence to conclude that ECT may be more effective than sham. At one month or longer, there is no evidence that ECT is superior to sham. A meta-analysis (random effects model) combining studies examining a two-week and four-week endpoint estimated that the mean improvement in Hamilton Depression Rating Scale (HDRS) for subjects treated with ECT was about 7.1 points (95% CI: -0.1, 14.2) greater than for those treated with sham therapy. A fixed effects model was also considered, and the effect of ECT was estimated to be 4.8 points (95% CI: 1.2, 8.4) greater than sham (See Figure 24).

b. ECT vs. Placebo for Depression

Immediately post-ECT, there is conclusive evidence to show that ECT is more effective than placebo. At six months post-ECT (long-term), one study demonstrated that ECT was more effective than placebo. Meta-analysis could not be conducted for this comparison.

c. ECT vs. Antidepressants for Depression

Immediately to one month post-ECT, there is conflicting evidence that ECT is more effective than antidepressant medication. At greater than one month post-ECT, there is conclusive evidence that ECT is more effective than antidepressant medication. A meta-analysis (random effects model) comparing ECT vs. antidepressant medications demonstrates that the mean improvement in HDRS for subjects treated with ECT was about 5.0 points (95% CI: 0.8, 9.1) greater than for those treated with some form of antidepressant therapy. A fixed-effects model was also considered, and the effect of ECT was estimated to be 5.1 (95% CI: 2.7, 7.6) points greater than antidepressant (See Figure 25).

d. Effect of Electrode Placement and Energy Dose for Depression

Electrode placement was classified as unilateral electrode placement (UL), right unilateral (RUL) and unilateral nondominant (ULND) were combined, and left unilateral (LUL) and unilateral dominant (ULD) were combined. Bitemporal (BT); or bilateral (BL) placement, if not further detailed) were combined, while bifrontal (BF) placements were treated separately. With regard to dosing, in seizure threshold titration protocols, stimuli just above seizure threshold (ST) to

1.5 times seizure threshold (1.5ST) were considered low energy, 1.5 to 3 ST were considered moderate energy and > 3 ST was considered high energy.

Immediately post-ECT to 2 weeks, there is evidence that there is probably no significant difference between BL (BT) and RUL (ULND) placement. No significant difference was seen between BF and RUL electrode placement. One study that examined ultrabrief pulse (UBP) stimulus and varying electrode placement demonstrated that UL UBP demonstrated significantly better effectiveness than BL UBP. After two weeks (and out to three months), there is conclusive evidence of no significant difference between BL and UL electrode placement.

In terms of energy dosage, high energy stimulation may be more effective than low to moderate energy stimulation (particularly when RUL electrode placement is used). There is conclusive evidence that across different treatment groups, a significant difference is seen pre- to post- treatment. This effect is demonstrated out to six months.

Three studies (n=128) demonstrated increased effectiveness of high energy dosing (especially with RUL electrode placement) versus moderate or low dose, while one study demonstrated no significant difference (n=67).

Nine studies (n=574) found a significant improvement between baseline and follow-up for individuals receiving any type of ECT treatment, with one study (n=27) demonstrating an effect as far out as six months. Meta-analyses were conducted examining electrode placement and energy dosage. Results are presented below:

- Bilateral vs. unilateral ECT (regardless of energy) (Figure 27)
    - Random effects: HDRS 4.0 points (95% CI: -0.6, 8.6) greater for BL vs. UL
    - Fixed-effects: HDRS 4.9 points (95% CI: 1.7, 8.0) greater fro BL vs. UL
- Bilateral ECT (low or medium dose) vs. unilateral ECT (high dose) (Figure 28)
    - Random effects: HDRS 0.2 points (95% CI: -2.2, 2.6) greater for BL vs. UL
    - Fixed effects: HDRS 0.2 (95% CI: -2.2, 2.6)

e. Effect of Treatment Frequency (2 times vs. 3 times per week) During a Course of ECT for Depression

Six studies were identified that compared the effectiveness of two times per week versus three times per week ECT during a course of treatment. These studies (n=133) demonstrated that at 1-4 weeks post-ECT course, both treatments demonstrated significant differences from baseline, but no significant differences

were demonstrated between groups. One study at one month post-course and one study at six months post-course continued to demonstrate no significant difference between the twice per week and thrice per week group. There was also conclusive evidence that three times per week treatment was associated with more rapid improvement in depression symptoms, though three times per week treatment was also associated with more severe memory problems.

A meta-analysis (random effects model) examining three studies that reported adequate information examining bilateral ECT two times per week (2x) or three times per week (3x) in the acute time period estimated that the mean improvement in HDRS for subjects treated with ECT three times per week was about 1.1 points (95% CI: -5.0, 7.2) greater than for those treated with ECT twice per week. A fixed effects model was also considered, and the effect was estimated to be 1.1 (95% CI: -2.9, 5.1).

f. Effect of Stimulus Modality (brief pulse vs. ultrabrief pulse)

Two RCT's examined the use of ultrabrief pulse stimulus in the treatment of depression. In one study (N=90), subjects were assigned to right unilateral ECT at six times seizure threshold or bilateral ECT at 2.5 times seizure threshold, and received either traditional brief pulse (1.5 msec) stimulus or ultrabrief pulse (0.3 msec) stimulus. At one week post treatment, ultrabrief pulse bilateral ECT was associated with significantly less improvement than the other three treatment arms (ultrabrief pulse unilateral, standard pulse unilateral or standard pulse bilateral treatment). In the other study (n=81), bifrontal ultrabrief pulse ECT at 1.5 times seizure threshold was compared with unilateral ultrabrief pulse ECT at six times seizure threshold. At one and six weeks post-treatment, there was no significant difference between the two groups (though the unilateral ultrabrief group required fewer treatments to achieve response/remission).

One RCT (n=42) compared the use of brief pulse versus ultrabrief pulse stimulus in the treatment of schizophrenia. All subjects in both groups experienced significant improvement from baseline immediately post-ECT and at 1 month post-ECT. However, there were no significant differences between groups at either time point.

g. ECT for Schizophrenia

In ECT vs. sham comparisons, the effectiveness of ECT and sham were not found to be significantly different. In ECT vs. sham augmentation of antipsychotic medication treatment, there is conclusive evidence that out to six months post-ECT, there was no significant difference between groups. But some evidence suggests that ECT augmentation of antipsychotic medication may be more effective than sham augmentation. These findings offer preliminary support for a conclusion that ECT may not necessarily be more effective than pharmacotherapy, but may increase the speed of response. A meta-analysis (Figure 26)

demonstrated that the mean improvement in Brief Psychiatric Rating Scale (BPRS) for subjects treated with ECT was about 2.3 points (95% CI: -3.7, 8.3) greater than for those treated with sham therapy. A fixed-effects model was also considered, and the effect of ECT was estimated to be 2.2 (95% CI: -2.0, 6.3).

h. ECT vs. Sham Studies for Mania

One study employed an ECT vs. sham design for the treatment of acute mania. This study demonstrated that ECT was significantly better than sham immediately post-ECT. Another study demonstrated that ECT was as effective as lithium in the treatment of mania immediately post-ECT.

i. Summary of Results of FDA Effectiveness Analyses

The following conclusions can be drawn regarding ECT effectiveness from this systematic review and meta-analysis of the literature:

- For depression (unipolar and bipolar), immediately post treatment, there is strong evidence that ECT is more effective than sham treatment.
- For depression, immediately post treatment, the difference in effect size (ECT vs. sham) is 4.8 to 7.1 points on the HDRS.
- For depression, after one month, the limited available evidence does not support the conclusion that that ECT is more effective than sham.
- For depression, immediately post treatment, there is strong evidence that ECT is more effective than placebo treatment.
- For depression, at six months post treatment, there is limited evidence that ECT is more effective than placebo.
- For depression, there is limited evidence that ECT is more effective than antidepressant medication within one month of treatment initiation. After one month there is strong evidence that ECT is more effective than antidepressant medication, demonstrating a mean five point greater improvement on the HDRS.
- If energy dosage is not taken into account, there is conflicting evidence that bilateral ECT is more effective than unilateral ECT, demonstrating a four point mean improvement in HDRS (compared to unilateral treatment). This meta-analysis result is contradicted by the systematic review conclusions and may be due to the fact that energy dosage was not accounted for in this initial meta-analysis.
- When energy is taken into account, low and moderate dose BL ECT appear to be similar in effectiveness compared to high dose RUL ECT.
- Limited evidence from the systematic review suggests that with RUL placement, high energy stimulus is more effective than moderate or low energy.
- There is limited evidence that immediately post-treatment, three times per week ECT may be slightly more effective than two times per week. This finding is supported by limited evidence supggesting that three times per week ECT may be associated with a more rapid rate of response. However, at longer time periods (i.e., 1 week to 6 months), two times per week ECT appears equally effective as three times per week ECT.

- For schizophrenia, limited evidence suggests ECT does not demonstrate greater overall effectiveness than sham, but may increase the speed of recovery.
- No conclusion can be drawn regarding the treatment of acute mania with ECT.
- Limited evidence suggests that high dose ultrabrief pulse ECT may be an effective treatment modality.

The Panel will be asked to consider whether there is sufficient evidence supporting the effectiveness of ECT for:

a. Depression,
   i. acute period (immediately post-treatment to one month),
   ii. longer term effectiveness (greater than one month)

b. Schizophrenia,
   i. acute period (immediately post-treatment to one month),
   ii. longer term effectiveness (greater than one month)

If longer term effectiveness of ECT is not demonstrated, is short term evidence alone adequate to support the effectiveness of ECT for these indications?

6. Specific Risks and Potential Mitigation Factors

6.1 Overview

To inform FDA's determination about the appropriate regulatory classification for ECT, FDA must identify the risks of the device. After the risks have been identified, FDA must determine whether sufficient information exists to establish regulatory controls – known as special controls – to mitigate those risks. Special controls can include guidance, labeling, device design requirements, conformance to performance standards, and other measures to provide a reasonable assurance of safety and effectiveness for the device type. Whether sufficient information exists to develop such controls will determine whether ECT should be reclassified into Class II or remain in Class III.

6.2 Comprehensive List of Potential Risks Associated with ECT Devices

The comprehensive list of potential risks identified by the FDA review team for ECT devices includes (in alphabetical order):

- Adverse reaction to anesthetic agents/neuromuscular blocking agents
- Alterations in blood pressure
- Auditory complications
- Cardiovascular complications
- Cognition (disorientation and confusion)
- Coma

- Death
- Dental/oral trauma
- Device malfunction
- General functional disability
- General motor dysfunction
- Homicidality
- Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
- Nausea
- Neurological symptoms
- Neuropathological changes
- Onset or exacerbation of psychiatric symptoms
- Pain/somatic discomfort
- Physical trauma
- Prolonged seizures
- Pulmonary complications
- Skin burns
- Sleep disturbance
- Stroke
- Substance abuse
- Suicidality
- Urinary complaints
- Visual disturbance

6.3 Identification of Key Risks

The FDA team, based on its comprehensive review, believes that the following key risks are the most significant and would need to be addressed to support reclassification into Class II (in alphabetical order):

- Adverse reaction to anesthetic agents/neuromuscular blocking agents
- Alterations in blood pressure
- Cardiovascular complications
- Cognition (disorientation and confusion)
- Death
- Dental/oral trauma
- Device malfunction
- Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
- Pain/somatic discomfort
- Physical trauma
- Prolonged seizures
- Pulmonary complications
- Skin burns

- Stroke

The Panel will be asked to consider whether the following risks are key risks of ECT devices, requiring the development of special controls:

a. Adverse reaction to anesthetic agents/neuromuscular blocking agents
b. Alterations in blood pressure
c. Cardiovascular complications
d. Cognition (disorientation and confusion)
e. Death
f. Dental/oral trauma
g. Device malfunction
h. Memory dysfunction (particularly retrograde autobiographical memory, anterograde memory)
i. Pain/somatic discomfort
j. Physical trauma
k. Prolonged seizures
l. Pulmonary complications
m. Skin burns
n. Stroke

Do any other key risks of ECT devices exist, and if so, what are the additional key risks?

6.4 Discussion of Key Risks and Potential Mitigation Factors

1. Cardiovascular, Pulmonary, and Anesthetic Risks including Stroke, Death Cardiovascular (arrhythmias, ischemia), pulmonary (prolonged apnea, aspiration), hemodynamic (hypertension, hypotension), anesthetic (adverse reactions) and stroke (hemorrhagic and ischemic) complications are relatively common and/or potentially severe adverse events of ECT. These complications make up the most frequent causes of significant morbidity and mortality associated with ECT. In order to mitigate the risk of these complications, pre-ECT medical evaluation assesses the risk of these conditions via pertinent history taking, physical examination and pertinent studies. Pre-treatment work-up may include:

    - EKG
    - Echocardiogram
    - Chest x-ray
    - Pulmonary function tests
    - Bronchoscopy
    - Laboratory tests
    - Neuroimaging

During ECT administration, monitoring of medical condition could be conducted via:

- EKG
- Blood pressure
- Pulse
- Respiratory rate

- Oxygen saturation

Clinical management may include determining whether ECT should be conducted, when it should be conducted, what precautions should be taken, and what clinical management should take place.

The Panel will be asked to consider whether the following requirements would adequately mitigate cardiovascular, pulmonary, and anesthetic risks (including stroke and death):

a. *Restricting ECT device use to physicians with specific training and/or experience with the administration of ECT;*
b. *Physician labeling recommendations for:*
    i. *pre-ECT assessment (including pertinent history taking, physical examination, EKG, echocardiogram, chest x-ray, pulmonary function tests, lab tests, and neuroimaging)*
    ii. *ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)*
    iii. *presence of an anesthesiologist during the ECT procedure*
c. *Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment*
d. *Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new IFU*

2. Memory and Cognitive Dysfunction

The FDA review found that ECT is likely associated with general memory dysfunction, most prominently anterograde memory loss and retrograde autobiographical memory, and immediate post-treatment cognitive dysfunction represented by disorientation. Disorientation appeared to be transient and generally resolved in a matter of minutes after the procedure. All memory domains, except autobiographical memory, appeared to resolve days to weeks after the completion of a course of ECT treatment. Autobiographical memory deficits were more persistent with evidence suggesting approximately 74% performance with RUL ECT and 58-66% performance with BL ECT at the one- to two-week time point. Limited evidence suggested that autobiographical memory deficits may approach baseline at six months.

Studies have demonstrated that potential mitigation factors for reducing the occurrence and risk of memory and cognitive adverse events might include:

- Exclusive use of square wave, direct current, brief pulse stimulus (vs. sine wave stimulus)

- Use of ultrabrief pulse (0.3 ms) stimulus (vs. sine wave or brief pulse (>0.3 ms)) stimulus
- Exclusive use of ULND electrode placement (vs. bilateral)
- Use of bifrontal electrode placement (vs. bitemporal)
- Use of the dose titration technique, and energy stimulation doses less than three times seizure threshold (vs. greater than or equal to three times seizure threshold)
- Limiting ECT administration to twice per week (vs. three times per week)
- When the onset of memory and cognitive dysfunction are noted, switching from bilateral to unilateral treatments, decreasing energy dose, or employing ultrabrief pulse (0.3 msec) stimulus

One of the special controls necessary for Class II designation would be the identification of safe stimulation parameters in the device labeling.

The Panel will be asked to consider whether the following labeling requirements would adequately mitigate memory and cognitive risks:

a. *Physician labeling recommendations for:*
    i. *Exclusive use of brief pulse (1-1.5 msec) waveform stimulus*
    ii. *Use of ultrabrief pulse (0.3 msec) stimulus*
    iii. *Exclusive use of unilateral nondominant electrode placement*
    iv. *Use of bifrontal electrode placement*
    v. *Limiting frequency of treatment to a maximum of twice weekly during a course of ECT*

b. *Patient labeling requiring use of a checklist of all known risks of ECT, with each item to be signed off by both patient and physician prior to initiating treatment.*
c. *Requirement for further premarket studies (either pre-clinical [bench, animal] or clinical) for significant changes in device technology or new IFU*

As noted for the first two key risks discussed above, a more rigorous informed consent process may be a useful special control for addressing the risks of ECT devices. The issue of inadequate informed consent processes and/or forced treatment has been raised in the public docket, in the MAUDE database and in the published literature. Critics of the process claim that if individuals are inadequately or inaccurately informed of the risks of ECT, the risk-benefit assessment is altered. One potential solution would be to outline a more rigorous consent process in the user labeling of the device that would require the use of an additional checklist (in addition to standard written informed consent procedures). This checklist would contain all known risks of device usage, the likelihood of occurrence and the potential severity. During the consent process, the treating physician and the patient would be required to review each item with both parties signing off to acknowledge discussion of the item. This checklist could then be kept with the standard written informed consent documentation. Within FDA, there is precedence for such additional informed consent requirements, as previous devices have also been approved with

requirements for such a checklist contained in user labeling (e.g., breast implants, implantable miniature telescope).

The Panel will be asked to consider whether patient labeling requiring use of a checklist, as part of the informed consent process, of all known risks of ECT, with each item to be signed off by both physician and patient, prior to initiating treatment would adequately mitigate adverse events such that the device could be classified a Class II device.

3. Prolonged Seizures

   Prolonged seizures, including status epilepticus, are infrequent, though potentially serious, adverse events associated with ECT. Individuals taking medications that lower the seizure threshold or suffering from conditions that lower the seizure threshold may be predisposed to suffer this adverse event. In order to mitigate this risk, pre-ECT evaluation includes a complete medical history, with neurological history, medication history, and review for conditions that may lower the seizure threshold. In addition, medications may be adjusted or conditions lowering the seizure threshold may be treated prior to the initiation of ECT. Finally, when a prolonged seizure is suspected, an EEG could be obtained to confirm the diagnosis.

The Panel will be asked to consider whether the following requirements would adequately mitigate the risk of prolonged seizures:

- *a. Restricting ECT device use to physicians;*
- *b. Requiring mandatory training for ECT practitioners;*
- *c. Labeling recommendations for medical management*
  - *i. Electroencephalography (EEG) monitoring during and after the procedure*
  - *ii. pre-ECT assessment (including pertinent history taking and physical examination);*
  - *iii. ECT procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)*
- *d. Requirements for animal and/or clinical studies for new device design/technology which could impact this risk of the ECT device type.*

4. Pain/Somatic Discomfort

   Pain and discomfort are relatively common, but are generally less severe adverse events related to ECT. Symptoms may include headache, somatic pain, and myalgias. While many patients may experience such symptoms, they are generally temporary and may be treated with analgesic medication.

The Panel will be asked to consider whether there should be labeling requirements recommending the clinically appropriate use of analgesic medication before, during or after the administration of ECT in order to adequately mitigate risks of pain and somatic discomfort.

5. Physical Trauma

In the past, physical trauma (e.g., such as orthopedic fractures, dislocations, or soft tissue trauma) were not uncommon complications of ECT. However with the use of general anesthesia and neuromuscular blockers, physical trauma is currently a rare event.

The Panel will be asked to consider whether there should be labeling requirements recommending the use of general anesthesia as part of the administration of ECT in order to adequately mitigate risks of physical trauma.

6. Skin Burns

   Skin burns may result from ECT at the site where the electrode contacts the skin. In the past, complaints of burns were not uncommon, but appear to be less common currently. Skin burns may be avoided with proper skin preparation, including the use of conductivity gel.

The Panel will be asked to consider whether there should be labeling requirements recommending proper skin preparation, including the use of conductivity gel, with ECT administration to adequately mitigate the risk of skin burns.

7. Dental/Oral Trauma

   Dental dislocations and fractures, and oral trauma are infrequent adverse events associated with ECT. These adverse events are caused by the contraction of the jaw muscles during ECT due to direct electrical stimulation which leads to clenching of the teeth and jaw. In order to mitigate this risk, pre-ECT dental evaluation is typically conducted to assess the risk of damage, and mouth protection ("bite blocks") is placed in the patient's mouth prior to stimulation.

The Panel will be asked to consider whether there should be labeling requirements recommending appropriate pre-ECT dental assessment and the use of mouth protection (bite blocks) in order to adequately mitigate the risk of dental and oral trauma.

8. Device Malfunction

   In addition to risks framed as adverse events affecting health status, risks may also be considered in the context of proper device function. Several MAUDE reports described device malfunction (n=5) or skin burns (n=17) that may have been due to faulty hardware or accessories (electrodes) or to improper use (see Section 6.4.6 above). Device malfunction may be a result of mechanical malfunction or software malfunction. In order to minimize device malfunction, established standards (ISO, ANSI) are available to help mitigate concerns regarding software development, bench performance testing, electrical safety and biocompatibility.

The Panel will be asked to consider whether the following manufacturing and testing guidelines would adequately mitigate the device-related risks of ECT devices:

a. electrical testing and adherence to recognized electrical standards

b. adherence to recognized software development standards
c. bench testing (to characterize device output)
d. biocompatibility testing (e.g. for electrodes) and conformance to recognized standards
e. electromagnetic compatibility (EMC) and electromagnetic interference (EMI) testing and conformance to recognized standards

For each of the key risks discussed above, the Panel will be asked to consider whether requiring further studies (either pre-clinical [bench or animal] or clinical) would aid in adequately assessing the risk and/or mitigation factor associated with the risk:

a. Cardiovascular, Pulmonary, Hemodynamic, Stroke, Death
b. Memory and Cognitive Dysfunction
c. Prolonged Seizures
d. Pain/Somatic Discomfort
e. Physical Trauma
f. Skin Burns
g. Dental/Oral Trauma
h. Device Malfunction

Table 15 summarizes the risks and proposed mitigation factors for risks associated with ECT.

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Table 1. 510(k) Applications for ECT Devices

Clearance Date	File	Sponsor	Device	Intended Use
06 Mar 97	K965070	Mecta	Spectrum 5000 q, 5000 m, 4000 q, 4000 m	"The intended use of the MECTA spECTrum ECT device is solely for the treatment of "severe depression or major depressive episode with melancholia". (ref 21 CFR Part 882 Part III) The clinical setting is in hospital ECT suites, Operating Rooms, or on patient wards."
18 Sep 96	K960754	Mecta	Spectrum 5000 q, 5000 m, 4000 q, 4000 m	"The intended use of the MECTA spECTrum ECT device is solely for the treatment of "severe depression" or "major depressive episode with melancholia". (ref 21 CFR Part 882 Part III) The clinical setting is in hospital ECT suites, Operating Rooms, or on patient wards."
1995	K955576	Somatics	Thymatron 2000 electroconvulsive system	"To treat patients suffering from depression, schizophrenia, and their manifestations."
26 Oct 95	K945120	Somatics	Thymatron 2000, electroconvulsive system, Thymatron system IV, Thymatron IV	"The primary indication is for major depression, however ECT is also indicated (in the labeling for this device) for schizophrenia."
18 Oct 91	K911144	Elcot	Mf-500, modification	"Electroconvulsive therapy device for treatment of severe depression only."
02 Jun 87	K863815	Elcot	Electroconvulsive therapy device, model	"The treatment of major depression and bipolar disorder, depressed phase. Also is effective for the treatment of patients in the manic phase of bipolar disorder, and for patients with catatonia."
10 Nov 86	K860467	Medcraft	Electroshock unit neurology model b-25	"The indication for use will be major depressive episodes with melancholia."
09 Aug 85	K852069	Mecta	Mecta ECT device models sr & jr	Major depressive episodes with melancholia.
03 Dec 84	K843923	Somatics	Thymatron	"For the treatment of certain serious psychiatric disorders, including especially major depression (with or without melancholia), bipolar affective disorder, and selected (e.g. acute, catatonic, schizophreniform, schizoaffective forms of non-chronic (type I)."

Table 2. Summary of Search Strategy Results

Topic Area	Number of Publications

Electroconvulsive Therapy (ECT)	9952
Major Depression (MD)	12317
Schizophrenia (S)	63845
Bipolar Disorder (BD)	883
Schizoaffective Disorder (SD)	72
Catatonia (C)	1220
Mania (M)	24536
Mixed Disorder (MXD)	144
Mood Disorder (MOD)	5413
After limits were Applied	
ECT and (MD or S or BD or SD or C or M or MXD or MOD), limit to English only	1984
Limit to clinical trial, Cochrane review, controlled clinical trials, meta analyses, randomized controlled clinical trials, systematic reviews, research study, cohort study, case-control study, cross-sectional study, case study, observational study and case report.	1231

Table 3. Adverse Events Reported in Public Docket

No.	ADVERSE EVENT
529	Memory complaint: short-term memory loss, chronic memory loss, permanent amnesia or missing blocks of time (years, months, etc.); inability to process, acquire, retrieve information
181	Cognitive complaint (confusion, delirium, encephalopathy)
94	Reduced intelligence/cognitive ability ("taming effect"), difficulty learning/reading/working; mentally incompetent
63	Unable to perform previous job skills, home activities, etc.
54	Apathy (sometimes with short-tem euphoria/giddiness), passivity, flattened affect; made tractable, compliant
9	Loss of creative ability
10	Unable to function socially
2	Dementia

296	Brain damage
1	Brain hemorrhage
1	Brain stem rupture
103	Death
43	Suicidality
23	Reduced life span
88	Worsening psychiatric complaint (e.g., depression, panic, fear, anxiety) reality: permanent incapacitation
82	"Vegetative" ("zombie") state; catatonia; loss of contact with reality; permanent incapacitation
67	Reduced quality of life, unspecified; life ruined, etc.*
28	Seizures
21	Physical trauma
10	Dental trauma
17	Cardiac/cardiovascular complications; or cardiac arrest
3	Hypertension
3	Cardiac arrhythmia
5	Stroke
15	Pain
13	Headache
12	Loss of fine motor skills, other motor skills
12	Damage to speech
9	Muscle twitching (dyskinesias)
2	Facial paralysis, reduced control of muscles
6	Muscle spasms, muscle aches
1	Muscle paralysis
9	Traumatized, unable to speak out
4	Emotional trauma, stigma from history of ECT treatment
7	Posttraumatic stress
7	Loss of various normal functions; dependent on care; etc.
7	Loss of balance, coordination
2	Falls
4	Sleep disturbance (e.g., nightmares)
4	Blindness; vision problems
1	Visual impairment
4	Nerve damage
4	Trigger for coma
4	Trigger for use of illicit drugs, alcohol, tobacco
4	Nausea/vomiting
3	Respiratory/pulmonary complications
1	Prolonged apnea
2	Burns
2	Homicidality
2	Loss of attention to personal hygiene
1	Abnormal sensations (parasthesias)

1	Permanent hair loss, follicle damage
1	Ruptured aneurysm
1	Compromised immune system
1	Fibromyalgia
1	Deterioration with incontinence
1	Chronic, loud buzzing sound in ears
3	Other (medical problems, etc)

Table 4. MAUDE Adverse Events Reports

By Adverse Event #	Adverse Event	Comments
117	Memory loss	
46	General emotional/psychiatric	
37	General motor	
35	General functional disability	
33	Headache	
30	Cognitive	Including learning disabilities
20	Seizures	
19	Pain	All types
17	Burns	one from faulty wire, and nonconductive gel
13	Neurological	All types not in other categories
10	Ineffective	
9	Brain damage	
8	Sleep disturbance	Including nightmares
8	Visual change	
6	Forced treatment	
6	Nausea	
6	Personality change	
5	Mechanical malfunction	
4	Cardiac	
4	Stroke	
3	Improper consent	
2	Death	one occurred within 2 mos of ECT
2	Auditory complaint	1-hyperacuity, 1-decreased acuity
2	Dental/oral	1-tongue laceration, 1-dental
2	Hypertension	
2	Hypotension	
2	Suicide	one was an attempt
2	Urinary complaint	1-incontinence, 1-frequency

2	Anesthesia-related	
1	Coma	
1	Miscarriage	
1	Pulmonary complication	

Table 5. Adverse Events Associated with ECT

Risk/Adverse Event	Types	Risk Characterized
Memory dysfunction	Anterograde verbal, Anterograde nonverbal, Retrograde autobiographical, Retrograde impersonal,	Generally memory dysfunction occurs, but resolves over time. Autobiographical memory dysfunction is longer lasting, with limited data suggesting complete resolution at 6 months.
Cognitive dysfunction	Orientation/reorientation, executive function, global cognition	Generally occurs post-treatment, but typically resolves minutes after completion of treatment.
Neuropathological changes	gross anatomical structural changes, neurohistological changes	Literature review suggests no evidence of anatomical structural, histological, immunohistological or biomarkers of injury. Some studies suggest neuroproliferative effect
Death/reduced life span		Literature review suggests mortality rate of 1:10,000 patient, or 1:80,000 treatments. This rate is on the order of minor surgical procedures.
Onset/exacerbation of psychiatric symptoms	Mood lability, manic switching, anxiety, panic/fear, subjective distress, personality changes, changes in motivation, apathy, catatonia, decreased responsiveness	Fairly common report in public docket responses, and MAUDE database. Causal attribution unclear.
General motor dysfunction	Weakness, tremor, gait disturbance, balance, residual muscle twitches	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited.
General functional disability	Problems attending to activities of daily living, work	Common complaint associated with ECT which may result in significant effects on the experience of the patient.
Pain/somatic discomfort	Headache, somatic pain, muscle soreness, dizziness	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited. May be treated with medication.

Prolonged seizures	Including status epilepticus	Rare reports in public, docket responses, MAUDE database and in the literature. May be exacerbated by medications and conditions that lower seizure threshold. Medical work up and management may mitigate risk.
Physical trauma	Fractures	Rare with the use of general anesthesia and neuromuscular blocking agents.
Skin burns	From poor electrode contact	Rare with proper skin preparation.
Neurological symptoms	Paresthesias, dyskinesias	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited.
Respiratory complications	Prolonged apnea, aspiration	Apnea related to slow metabolism of succinylcholine. May use alternative nondepolarizing muscle blocker. Aspiration an uncommon, but known risk of general anesthesia.
Sleep disturbance	Nightmares	Rare reports in public docket responses and MAUDE database.
Visual disturbance	Impairment, changes, corneal abrasion	Rare reports in public docket responses and MAUDE database.
Nausea		Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited. May be treated with medication.
Alterations in blood pressure	Hypotension, hypertension	Hypertension a known very common risk of ECT.Risk may increase with co-morbid medical conditions. Hypotension a common risk of ECT, may be due to underlying cardiac disease or iatrogenic. Medical work up and management may mitigate risk.
Cardiovascular complications	Arrhythmias, ischemia	Known common risk of ECT. Risk may increase with co-morbid cardiac condition. Medical work up and management may mitigate risk.
Stroke	Hemorrhagic or ischemic	Rare reports in public, docket responses, MAUDE database and in the literature. Risk may increase with co-morbid intracranial pathology.Medical work up and management may mitigate risk.
Auditory complications	Decreased acuity, hyperacuity, tinnitus	Rare reports in public docket responses and MAUDE database.
Dental/oral trauma	Dental fractures, lacerations, bleeding	Rare reports in public docket responses and MAUDE database.
Suicidality	Ideation and attempts	Rare reports in public docket responses and MAUDE database. No indication of increased

		risk in the literature, and some suggestion that risk may decrease.
Homicidality	Ideation and attempts	Rare reports in public docket responses and MAUDE database. No indication of increased risk in the literature.
Substance abuse	Use of illicit drugs	Rare reports in public docket responses and MAUDE database. No reports in the literature. Causal attribution unclear
Urinary complaints	Hesitancy, incontinence	Some reports in public docket responses and MAUDE database. Symptoms are generally not severe and time-limited.
Coma		Some reports in public docket responses and MAUDE database.
Iatrogenic	Adverse reaction to anesthetic agents/neuromuscular blocking agents	Rare reports in public docket responses, MAUDE database, and literature. Risks of general anesthetic agents and neuromuscular blockers known. Risk is low, but potentially severe.

Table 6. RCTs Included in Systematic Review of Memory and Cognitive Adverse Events

First Author	Year	Subjects	N	Comparison	Time after ECT (completion of course)	Cognitive Measure	Change from baseline	Outcome difference between groups	Comment
Abrams	1967	Acute SCZ (<3 months)	10	ULND 3x/week vs. ULND 5x/week	Within 8 hrs. of last ECT	WMS minus visual subtest	NST	NSS	No cognitive differences between groups
Ayuso-Gutierrez	1982	Endogenous depression	22	CDP-choline vs. placebo in BL ECT	Within 24 hrs. after 4th ECT	Time to reorientation; TEA memory test —digits and associative, based on Weschler subscales	NST for all measures	NSS for all measures	No benefit to CDP-Choline for ECT- induced memory dysfunction
Bagadia	1981	Depression (20 ss), SCZ (20 ss)	40	BL+ placebo vs. BL + imipramine (depression) or chlorpromazine (SCZ)	48 hours	Arithmetic test; Kohs Block Design; Picture recog-nition	SCZ group declined SS on Arithmetic test; all improved SS on Kohs; other measures NSS	NSS for all measures	No deficits felt to be clinically significant
Bailine	2000	MDE DSM-IV unilateral or bipolar	48	BF vs. BT	24 hours	MMSE	BF exactly same; BT declined SS	BT worse— SS	BF as efficacious as BT with less cognitive impairment
Barekatain	2008	DSM-IV mania	28	BF 1.5x threshold vs. BT 1x	2 days	MMSE	Declined— significant interaction between group and time	BT worse—SS	BF as effective as BT with fewer cognitive side effects
Bauer	2009	MDD, ICD10	62	BL propofol anesthesia vs. BL thiopental anesthesia	5 days	MMSE	NST	propofol worse— SS	More severe cognitive effects with propofol
Bidder	1970	Depressed, no SCZ, left cerebral dominant	96	BL vs. UL	All measures post ECT 2, 4, 6; PALT and Benton also given at 30 days and 1 year	PALT; Benton visual retention test; Personal Data sheet	PALT: SS declined initially; NSS by 10 days, SS improved by 30 days Benton: NSS initially, SS improved at 30 days, NSS at 1	PALT BL worse initially, NSS by 10 days Benton: NSS Personal Data Sheet: BL worse after ECT 6—SS	UL less memory impairment initially but required more treatment sessions for response

							year Personal Data Sheet: SS declined over course of ECT		
Chanpattana	1999	Treatment resistant SCZ	51 (45 completed)	BL C-ECT + flupenthixol vs. BL C-ECT vs. flupenthixol	1 week	MMSE	NST	NSS	Continuation ECT study; med + ECT group best at relapse prevention with same global cognitive outcome
Chanpattana	2000	DSM-IV SCZ	62	BL 1x threshold vs. BL 2x vs. BL 4x	1 week	MMSE	NST	NSS	High dose speeds response, no global cognitive difference
Coffey	1990	DSM-III MDE including bipolar (n=7) and SCZ-AFF (n=1)	40	Caffeine augmentation vs. stimulus intensity dosing; UNLD with nonrandomized crossover (n=7) to BL	2-3 days	WMS delayed verbal and figural scales	NST	NSS	No difference in therapeutic outcome or cognitive side effects with caffeine
Cohen	1968	R handed females, affectively depressed	24	LUL vs. RUL vs. BL	5-8 hours after ECT 5	Verbal paired associates; Visuographic learning task (learning trial presented pre-ECT for both measures)	NST	BL worse than UL both measures—SS	Larger verbal than non-verbal decrement in LUL, opposite pattern in RUL
Costello	1970	depressive	30	ULND vs. ULD, vs. BL	29-31 hours	Paired words	NST	ULD worse than ULND—SS; BL worse than ULD or ULND—SS	No therapeutic differences between groups, ULND best cognitive outcomes
Cronin	1970	Females; Endogenous, reactive depression	51	ULND vs. ULD vs. BL (6/8 ECTs)	Acute; 24 hrs. after ECT 8; 4-6 weeks	Confusion clinician rating; MWLT; Graham-Kendall; Benton; WMS Part I—Personal and Current Info	NST all measures	Confusion: BL worse—SS MWLT: ULND best at 4-6 weeks only—SS WMS Personal: ULND best at 24 hours and 4-6 weeks—SS All other measures NSS	ULND least acute confusion, less verbal memory disturbance than BL or ULD; but BL better therapeutic benefit in endogenous group only
D'Elia	1978	Pervasive depressed mood	44	L-tryptophan + ULND vs. placebo + ULND	4 days	30 word pair test, 30 geometrical figure test, 30 face test; 30 figure test:	Word pair: L-TP all NSS; Placebo group immediate memory—	Face: forgetting score worse L-TP—SS All others— NSS	Memory possibly worse with L-TP

						immediate memory, delayed memory and forgetting score	NSS, delayed memory declined— SS, forgetting improved—SS Figure: L-TP improved immediate + delayed—SS, forgetting NSS, placebo all NSS All other measures: NSS		
D'Elia	1970	Endogenous depression	53	BL vs. ULND	3-7 days, 1 month	Subjective rating scale	--	NSS	
Dubovsky	2001	DSM-IV MDD, medication refractory	26	Randomized to Nicardipine vs. placebo; UL/BL non randomized	Acutely and 6 months	Trail A + B, Digit span, FAS verbal fluency, MMSE, WMS-R, Digit symbol, California Verbal Learning Test (CVLT), animal recognition	Trail B: Nicardipine group only declined acutely—SS Trail A: improved at 6 months—SS FAS: declined acutely, returned to baseline at 6 months— SS All others NSS	All NSS	
Eschweiler	2007	Treatment resistant MDE	92	RUL 2.5x threshold vs. BF 1.5x	1 day	Modified MMSE, MMSE, Thurstone Word Fluency Test (TWFT), CFT, Labyrinth test	TWFT , CFT declined — SS Labyrinth test improved— SS All others NSS	CFT: RUL worse-SS All others NSS	
Fleminger	1970	Depression, right handed	36	LUL vs. RUL vs. BL	3 days	WMS minus visual subtests	NST	UL left worse vs. right UL—SS; on PALT subtest, LUL also worse vs. BL—SS	
Fraser	1980	Depression (Feighner) Age 64-86	29	ULND vs. BL	Acutely, 3 weeks	Time to reorientation, WMS-I, WMS-O, WMS-D, WMS—MC, WMS—memory passage, WMS—	Time to reorientation: UL improved ECT 1 to 5— SS WMS-I: BL improved at 3	Time to reorientation: BL worse —SS All others NSS	

						associate learning, WMS-VR	weeks—SS WMS-MC: both improved at 3 weeks—SS Memory passage: ULND improved at both times—SS Associate learning, VR: BL improved at both times—SS All others NSS		
Frith	1987	Severe endogenous depression	70	8 real vs. 8 sham BF	Acutely, 2 days	Word list recall + recognition, face-label, sentence verification, famous names	Sentence verification: both improved acutely—SS Famous names: sham worse acutely—SS All others NSS	Word list recognition at 2 days: real ECT worse—SS Face label real worse acutely—SS Sentence verification, famous names: sham worse acutely—SS All others NSS	
Frith	1983	Severe endogenous depression	70	8 Real vs. 8 sham BF	Acutely, 1 + 6 months	Kornetsky-Mirsky CPT, word labels for faces, word list recall + recognition, famous names, patient endorsed memory problem	Word list recognition: real declined at 1 month—SS Patient endorsed memory problem: both declined at 6 months—SS All others NSS or NST	Word list recognition: real worse—SS Sham ECT worse at 1 month—SS All others NSS	Patient endorsed memory problem: fewer memory complaints at 6 months when positive treatment response for depression—SS
Geretsegger	2007	Severe MDD	50	ECT propofol vs. ECT methohexital	2 months	STGI short test for general intelligence (STM), SST syndrome short test	NST	NSS	
Halliday	1968	Depression	52	LUL vs. RUL vs. BL	Acutely, >2 days, 3 months	Time to reorientation, digit span, verbal learning, non verbal learning	All NST	Time to reorientation: BL worse than LUL worse than RUL—SS Digit span: LUL worse than RUL at 2 days, BL worse than RUL at 3 months—SS Verbal learning: LUL worse	

								than RUL/BL at 2 days, worse than RUL at 3 months—SS Non verbal learning: LUL worse than RUL at 2 days and 3 months—SS Delayed nonverbal: BL worse than RUl at 3 months—SS All others NSS	
Heikman	2002	MDE; no SCZ, SCZ-AFF, or BPD-RC	24	RUL 4x threshold vs. RUL 1.5x vs. BF 1x	1-3 days	MMSE	NST	NSS	
Heshe	1978	Depression	75 (but 50 or fewer completed each measures)	UL vs. BL	1 week, 3 months	Story recall, PALT, picture recognition, visual reproduction, Kumura figures, face recognition, tactile maze	NST	Picture recognition: BL worse at 1 week but BL better at in immediate condition at 3 months—SS All others NSS	
Hiremani	2008	Mania	36	BF vs. BT	acutely	TMTA, TMT, verbal fluency, MMSE, CFT	All NST	All NSS	
Horne	1984	MDD DSMIII	48	BL placebo vs. BL dexamethasone vs. RUL placebo vs. RUL dexamethasome	24 hours	Digits forward, TMT-B, random number generation, STM story recall, PALT, object memory, Rey Davis, ROCF	All NST	Digits forward, TMT-B, STM: dexamethasone worse—SS All others NSS	
Horne	1985	DSM-III MDD	48	ULND vs. BL; dexamethasone vs. placebo	1-2 days	Trail B, digits forward + backward, random numbers, WMS-PALT, WMS-ss, CFT	Trail B, digits backward: UL improved—SS WMS-ss, CFT: BL declined—SS All others NSS	Digits backward, random numbers, PALT, WMS-ss, CFT: BL worse—SS All others NSS	
Jackson	1978	Right handed males referred	46	LUL vs. RUL vs. BL vs. no-ECT	Acutely, 10 days	WMS minus visual	All WMS minus VR subtests except	All ECT groups worse than control on WMS minus VR,	

		for ECT		control		reproduction, WVLT, WMS-VR, Williams visuospatial (Rey Davis)	digits forward + backward, logical memory, and WVLT, Williams declined acutely (but NSS at 10 days)— SS Williams declined acutely—SS All others NSS	Williams acutely only—SS WVLT: BL/LUL worse than RUL—SS WMS-VR: BL worse than control—SS All others NSS	
Janicak	1991	depressed	27	ULND vs. BL	3-5 days, 6 months	VPA, CFT, famous events, famous faces	VPA, CFT, famous events declined at 3-5 days only — SS All others NSS	All comparisons NSS	First 8 subjects nonrandomly assigned to ULND
Kellner	2006	DSM-IV unipolar depression	201	continuation-ECT vs continuation-medications (lithium + nortriptyline)	3, 6 months	mMMSE	Improved-- SS	NSS	
Kellner	1992	DSM-III MDD Age 53-87	15	BL 1x/week vs. BL 3x/week	1 week	MMSE, WMS subtests: attention, verbal + visual + general memory	All tests NSS	All comparisons NSS	
Kellner	2010	MDE	230	RUL 6x threshold vs. BF 1.5x vs. BT 1.5x	Reorientation acutely, other tests 1-2 days	Reorientation, Stroop, Trail A+B, D-KEFS, MMSE, RAVLT, COWAT, category fluency, CFT, AMI-SF	All NST	Reorientation: RUL best, BF worst—SS RAVLT: BF worse than BT—SS All others NSS	
Langer	1995	Treatment resistant MDD, DSM-III	20	BT vs. ISONAR (isoflurane anesthesia)	2 weeks	ACOT, Pauli, GVM-A+C, Benton	ACOT variability: BT worse— SS Pauli: ISONAR improved—SS GVM-A: both improved—SS GVM-C: ISONAR improved, BT declined—SS Benton: ISONAR	ACOT variability, GVM-C: BT worse—SS All others NSS	

							same, BT improved—SS All others NSS		
Levy	1968	depression	40	UL vs. BL (6 ECTs)	6 hours after last ECT	Gresham-GO +GE + RPE, WMS, PALT,	All declined—SS	All groups NSS Gresham GO+ GE: BL worse on group x time interaction	
Lisanby	2000	MDD; non randomized controls	55	RUL vs. BL, low vs. high dose; normal controls	1 week	PIMT-I, PIMT-P	PIMT-I: ECT declined—SS; controls same—NSS PIMT-P: ECT declined; controls same –SS	All measures: BL worse--SS; dose no effect—NSS	
Martensson	1994	MDD DSM-III (47), other (6)	53	ECT propofol Ect methohexital	Acutely, after 3 days	Verbal Fluency (FAS), MMSE, WMS, Buschke SRT, Claeson-Dahl learning and retention, ROCF copy + recall, Corsi, Knox	MMSE decreased acutely only—SS WMS 24 hour recall, ROCF copy decreased acutely—SS All others NSS	All NSS	
Mattes	1990	MDE, DSM III	33	BT vasopressin vs. BT placebo	1 day after ECT 5	digit span, PALT, ROCF, TV test (retrograde), subjective memory rating form	PALT, ROCF decreased—SS Subjective memory #9-16 improved—SS All others NSS	All NSS	
McAlister	1987	DSM-III MDE	20	UL 2x/week vs. UL 3x/week	2 weeks	WMS visual memory, Porteus mazes	WMS: improved—SS Porteus—NSS	WMS: 3x/week worse—SS Porteus—NSS	
McCall	2002	MDD; no SCZ, SCZ-AFF, substance abuse, MR, or neuro problems	77	RUL 8x threshold vs. BL 1.5x	1-3 days, 2 weeks, 4 weeks	RAVLT, CFT, PMQ	All NST	All NSS	
McCall	2000	MDD	72	RUL 2.25x threshold vs. RUL fixed high dose	Acutely for reorientation, 1-2 days for	Time to reorientation, MMSE, RAVLT,	All NST	Time to reorientation, MMSE. Duke: Fixed high dose worse—	

					others	CFT, Duke, patient memory rating scale		SS All others NSS	
McDonald	1966	depression	30	ECT vs. amitriptyline vs. sham ECT or placebo	1 week	WBPIQ, Bender-Gestalt, WBVIQ	All NST	All NSS	
McElhiney	1995	MDD-RDC; non depressed controls	75	RUL vs. BL; Low vs. high dose	1 week	AMI	NST	BL worse—SS; Dose—NSS Depressed worse than controls at baseline—SS	
Mohan	2009	mania	50	BL brief pulse at threshold vs. 2.5x	2 weeks	WMS, MMSE, autobiographical question bank	MMSE—NSS All others: NST	WMS, autobio questions: NSS MMSE: NST	
Pettinati	1984	DSM-III MDD	28	ULND vs. BL	1 day	SSMQ	Improved--SS	BL worse--SS	
Prakash	2006	MDD, SCZ, Delusional, BPD, psychosis nos	45	ECT + donezepil vs. ECT + placebo	Acutely after each of 8 ECTs	Modified MMSE subtests: alertness, obey commands, repetition, impersonal + personal memory	NST	SS: donezepil better in some sessions all subtests—SS	
Rami	2008	DSM-IV depression, BPD, SCZ, SCZ-AFF	24	Single maintenance ECT vs. control maintenance-ECT	90 minutes	Short portable mental status questionnaire, Verbal phonetic fluency (Borkowski), WAIS-III digits forward + backward, list learning based on RAVLT	All NSS	All NSS	
Ranjkesh	2005	MDE	45	RUL 5x threshold vs. BF 1.5x vs. BT 1x	1 day	MMSE	Declined-SS	BT and RUL worse than BF--SS	
Rosenberg	1984	DSM-III MDD or SCZ-AFF	35	ULND vs. BL	1 week	Structured interview of subjective memory	N/A	BL worse—SS	
Sackeim	2009	MDD, BPD, DSM	319	RUL high vs. BL medium; nortriptyline vs.	1-2 days	N back D, MMSE, BSRT, AMI-SF	All NST	BSRT, AMI-SF: BL worse—SS All others NSS for RUL vs.	

				venlafaxine vs. placebo				BL	
Sackeim	1993	MDD-RDC	96	RUL vs. BL; low vs. high dose (at threshold vs. 2.5x)	1-2 days	Time to reorientation, paired words + faces, SRT, MMSE, AMI, SSMQ	SSMQ: all groups improved-- SS; correlated with depression response All others NST	Time to reorientation, paired words: BL, high dose worse--SS SRT, MMSE, AMI: BL worse—SS All others NSS	
Sackeim	2000	MDD-RDC; no SCZ, SCZ-AFF, or BPD-RC	80	RUL 0.5x, 1.5x, 5x threshold vs. BL 1.5x	1 week	Time to reorientation, modified MMSE, BSRT, paired words + faces, Randt paired words + short story+ picture recall, CFT, Goldberg-Barnett famous events, AMI, SSMQ	SSMQ: All groups improved--SS All others NST	Time to reorientation: RUL high worse than RUL low/med; BL worse than any RUL—SS mMMSE, BSRT, paired words, Randt picture recall, famous events, AMI: BL worse—SS Randt short story, CFT: High dose RUL + BL worse than low/ mod RUL--SS All others NSS	
Sackeim	2008	MDD-RDC; no SCZ, SCZ-AFF, or BPD-RC	90	RUL 6x vs. BL 2.5; brief pulse 1.5 ms vs. UBP 0.3 ms	Acutely, 1 week	Time to reorientation, cancellation, verbal fluency, MMSE, word recall+recognition, sentence recognition + temporal order, BSRT, Randt story recall, shape recognition, neutral face recognition, affective face recognition, CFT, Goldberg Barnett, AMI, patient memory rating	Patient memory rating: all groups declined at 1 week—SS All others NST	Time to reorientation: Brief pulse worse vs. UBP--ss; BL worse vs. RUL—SS Cancellation performance, some verbal fluency/nam ing tasks, word recall+recogntion, sentence recognition, shape, neutral face, affective face: Brief pulse worse vs. UBP acutely—SS MMSE, BSRT, CFT: Brief pulse worse vs. UBP at 1 week—SS Randt story recall, Goldberg Barnett, AMI, patient memory rating: Brief pulse worse at 1 week--ss; BL worse at 1 week--ss All others NSS	
Shapira	2000	MDD, endogenous	47	BL 2x/week + 1sham/week vs. BL	24 hours, 3 days, 1 month	Global battery at 3 days:	Global battery: Both groups	overall and on anterograde faces, digits	

		subtype		3x/week; uncontrolled # of ECT		orientation, WAIS + retrograde task Global battery at 24 hours and 1 month: CFT, VPA, verbal vs visuospatial recall, immed memory, Famous Events, PMQ	declined at 24 hours and 3 days—SS Global battery at 1 month: NSS	backward,retrograde word list: 3x/week worse at 3 days—SS Verbal + verbal vs visuospatial recall, delayed visuospatial recall subtests: 3x/week worse at 24 hours, 1 month—SS (Other subtests NSS)	
Sienaert	2010	DSM-IV MDE	64	UBP BF 1.5 x threshold vs. UBP UL 6x	Acutely, 1 week, 6 weeks	Time to reorientation, CPT, LNS, Trail A+B, WCST, MMSE, RAVLT, AMI, SSMQ	CPT, WCST, MMSE, RAVLT, AMI at 1 +6 weeks; SSMQ at 1 week: Improved--SS All others NSS	All NSS	Lower SSMQ correlated with higher depression symptoms on HRSD
Small	1968	SCZ, affective, organic disorders	100	Sine ECT vs. inhaled flurothyl	1 week	WMS—memory quotient	NST	Sine ECT worse—SS	
Smith	2010	DSM-IV MDD	85	BL continuationECT vs. nortriptyline +lithium	12 and 24 weeks	RAVLT, CFT, AMI, SSMQ	RAVLT, CFT: Both improved at 12 and 24 weeks—SS AMI: C-pharm improved at 12 weeks only—SS SSMQ: both improved at 24 weeks only—SS All others NSS	AMI: C-ECT worse at 12 weeks only—SS All others NSS	
Sobin	1995	MDD-RDC	71	RUL vs. BL; low vs. high dose	Acutely, 1 week	Time to reorientation, MMSE, AMI	MMSE at 1 week: BL declined—SS Others NSS or NST	Time to reorientation: BL worse—SS; high dose worse—SS MMSE (acute + 1 week), AMI (1 week): BL worse—SS Dose comparisons: NSS	
Stoppe	2006	MDD Age >60	39	RUL vs. BL modified fixed high dose	1day, 1 month	MMSE, digits forward + backward, WAIS-R vocabulary,	MMSE: NST All others NSS	MMSE at 1 day: BL worse All others (at 1 month): NST	

						WAIS-R block design/clock drawing, Brazilian autobiographical memory scale			
Strain	1968	Depressed; including manic-depressive, psychotic	102	RUL vs. BL	36 hours, 10 days	PALT, Revised Benton, personal data sheet for recent+ remote memory	PALT, personal data sheet: declined at 36 hours—SS, NST at 10 days Benton: NSS	PALT: BL worse—SS at 36 hours, NSS at 10 days Personal data sheet: BL worse at 36 hours--SS, NST at 10 days Benton: NSS	
Tang	2002	DSM IV MDD or SCZ	38	BL + piracetam vs. BL+ placebo	2 weeks	WMS-R VPA + visual reproduction, CFT, AMI (2 subtests removed), SSMQ	All NST	All NSS	
Taylor	1985	DSM-III melancholia	37	ULND vs. BL	2-3 days	Global battery including MMSE	NSS	NSS	
Tew	2002	DSM-III-R MDE Age 50+	24	BL vs. high charge RUL after 5-8 failed moderate charge RUL	1-3 days	MMSE	NST	BL worse— SS	
Warnell	2010	DSM-IV-TR MDD without psychosis Age 45+	15	BT + propofol interruption post seizure vs. BT + placebo	24-36 hours	WMS subscales: Letter number sequencing, verbal paired associate, immediate memory, auditory immediate + delayed, visual immediate, faces	All others NSS	Immediate memory, auditory delayed: BT+ propofol better—SS All others NSS	
Warren	1984	depression	54 (38 completed)	High energy sine vs. high energy pulse vs. low energy pulse	24 hours, 2 weeks	WMS subscales: digits forward + backward, logical memory; Warren verbal recognition; Warrington facial recognition	Digits forward + backward at 2 weeks: NSS Logical memory at 2 weeks only: High sine improved— SS; high pulse improved on 1	All NSS	

							story— SS Verbal recognition at 2 weeks: high sine improved— SS Facial recognition at 2 weeks: all improved—SS		
Weaver	1977	Endogenous depression, medication nonresponse	20	Low energy BP vs. sine	Unclear interval after ECT	Halstead Reitan, Wechsler Bellevue IQ	Halstead Reitan NST; Wechsler NSS	All NSS	
Weiner	1986	MDD-RDC	74	Sine vs. brief pulse; UNLD vs. BL; vs. inpatient psychiatric controls with similar diagnoses	2-3 days, 6 months	VPA, WMS-P, CFT, unfamiliar faces, famous events, famous faces, personal memory questionnaire, modified SSMQ	VPA, WMS-P, famous faces at 2-3 days: BL and sine worse than controls— ss Famous events at 2-3 days: BL worse than controls— SS CFT at 2-3 days: BL, ULND, and sine worse than controls—SS All NSS at 6 months except: personal memory declined—SS All others NSS	VPA, famous events, famous faces, personal memory at 2-3 days: BL worse—SS; Sine worse— SS WMS-P at 2-3 days: BL worse vs. control—SS; sine worse— SS CFT at 2-3 days: sine worse— SS All NSS at 6 months except personal memory: BL worse; sine worse vs. controls— SS All others NSS	Improvement in SSMQ correlated with depression improvement
Zinkin	1968	Depressive illness, inpatient/outpatient	102	UL vs. BL	2 hours after ECT	Picture recognition	NST	BL worse—SS	

Abbreviations:

BF	Bifrontal ECT
BL	Bilateral ECT
BPD	Bipolar disorder
BPD-RC	Bipolar disorder, rapid cycling
BT	Bitemporal ECT
C-ECT	Continuation ECT
ECT	Electroconvulsive therapy
LUL	Left unilateral ECT
MDD-RDC	Major depressive disorder (Research Diagnostic Criteria)
MDE	Major depressive episode (DSM); unipolar or bipolar
NSS	Not statistically significant
NST	No valid statistical test conducted
RCT	Randomized controlled/comparison trial
RUL	Right unilateral ECT
SCZ	Schizophrenia
SCZ-AFF	Schizoaffective disorder
SS	Statistically significant
UBP	Ultra brief pulse ECT
ULND	Unilateral non-dominant ECT
ULD	Unilateral dominant ECT

Tests (abbreviations):
General Orientation subtest of Gresham Battery (Gresham-GO)
Stroop Color-Word Interference (Stroop)
Continuous Performance Task (CPT)
Kornetsky-Mirsky Continuous Processing Task
Trail Making A and B Test from Halstead Reitan Battery
Letter Number Sequencing Test (LNS)
Wisconsin Card Sorting Test (WCST)
Delis-Kaplan Executive Function Sorting Test (D-KEFS)
Alphabetic Cross-Out Test (ACOT)
Weschler Memory Scale (WMS) subtests: orientation (WMS-O), mental control (WMS-MC), and Digits (WMS-D), paragraph retention (WMS-P), Short Story (WMS-SS), verbal (WMS-V), visual reproduction (WMS-VR)
Buschke Selective Reminding Test (BSRT)
Selective Reminding Test (SRT)
Paired word and short story recall, picture recall portions of the Randt Memory Test
Rey Auditory-Verbal Learning Task (RAVLT)
Williams Verbal Learning Test (WVLT)
Modified Word-Learning Test (MWLT)
Paired Associates Learning Test (PALT)
Other Verbal Paired Associates (VPA) or word recall tasks
Controlled Oral Word Association Test (COWAT)
Grunberger Verbal Memory Test—Associative Memory (GVM-A)
Grunberger Verbal Memory Test—Common Memory (GVM-C)
Wechsler-Bellevue Intelligence Scale—Verbal IQ (WBVIQ), Performance IQ (WBPIQ);
Complex Figure Test with copy and recall of figures such as the Rey-Osterreith, Taylor, Ritchie, Medical College of Georgia Complex Figures (CFT)
Graham-Kendall Memory for Designs Test (Graham-Kendall)
Benton Visual Retention Test (Benton)
Labyrinth subtest of the Nurnberg Age Inventory
Bender-Gestalt Test
Koh's Block Design Test
Goldberg-Barnett Remote Memory Questionnaire (Goldberg-Barnett)
Personal and Impersonal Memory Test, impersonal component (PIMT-I)
Personal and Impersonal Memory Test, personal component (PIMT-P)
General Events subtest of Gresham Battery (Gresham—GE)
Weschler Memory Test Information subscale (WMS-I)
Squire Subjective Memory Questionnaire (SSMQ)

Table 7. Autobiographical Memory – RCTs Reporting Change from Baseline Data

Author	Year	Comparison	N	Time post ECT	Measure	% Recall (or 100 - % amnesia)
Sackeim	1993	RUL vs. BL; low vs. high dose (at threshold vs. 2.5x)	96	1-2 days	AMI	RUL low 81% RUL high 82% BL low 66% BL high 76%
McElhiney	1995	RUL vs. BL, Low vs. high dose No crossover Data from graph	75	1 week 2 month	AMI	RUL 1 w: 69% BL 1 w: 62% RUL 2 mo: 74% BL 2 mo: 69%
Sobin	1995	RUL vs. BL; low vs. high dose % inconsistent reported (100 – x)	71	1 week	AMI	RUL low 69% RUL high 73% BL low 53% BL high 62%
Sackeim	2000a	RUL 0.5x, 1.5x, 5x threshold vs. BL 1.5x	80	1 week	AMI	RUL 0.5ST 70% RUL 1.5ST: 70% RUL 5ST: 61% BL 1.5 ST: 42%
Sackeim (Electrophysiological Correlates)	2000b	RUL ST RUL 2.5ST BL ST BL 2.5ST Reported as % amnesia (100 – x)	59	1 week	AMI	RUL ST 76% RUL 2.5ST 75% BL ST 57% BL 2.5ST 62%
Sackeim	2008	RUL 6x vs. BL 2.5; brief pulse 1.5 ms vs. UBP 0.3 ms	90	Post-course	AMI	RUL UBP 94% RUL BP 90% BL UBP 94% BL BP 78%
Lisanby	2000	RUL vs. BL, low vs. high dose	55	1 week	PIMT-P Strong concurrent AMI validity	RUL: 90% BL: 72% Reported as % change from baseline
Weiner	1986	Sine vs. brief pulse; UNLD vs. BL; nonrandomized controls	74	2-3 D 6 Mo	PMQ	2-3 D PUL 80% SUL 58% PBL 55% SBL 40% Control NR 75% 6 M PUL 82%

						SUL 78% PBL 70% SBL 60% Control NR 83% 6 M with corroboration PUL 90% SUL 89% PBL 80% SBL 70% Control NR 92%
McCall	2000	RUL 2.25x threshold vs. RUL fixed high dose	72	1-2 days	Duke	66% recall 2.25x 54% fixed high
McCall	2002	RUL 8x BL 1.5x	77	1-3D 2 w 4w	PMQ	RUL 8ST: 56% BL 1.5ST: 64%

AMI = autobiographical memory interview
PMQ = personal memory questionnaire
Duke = Duke peronsal memory questionnaire
PIMT-P = Personal and impersonal memory test-personal section
RUL = right unilateral
BL = bilateral
ST = seizure threshold
BP = brief pulse
UBP = ultrabrief pulse
PUL = pulse unilateral
SUL = sine unilateral
PBL = pulse bilateral
SBL = sine bilateral
NR = nonrandomized

Figure 1. Public Docket Respondents

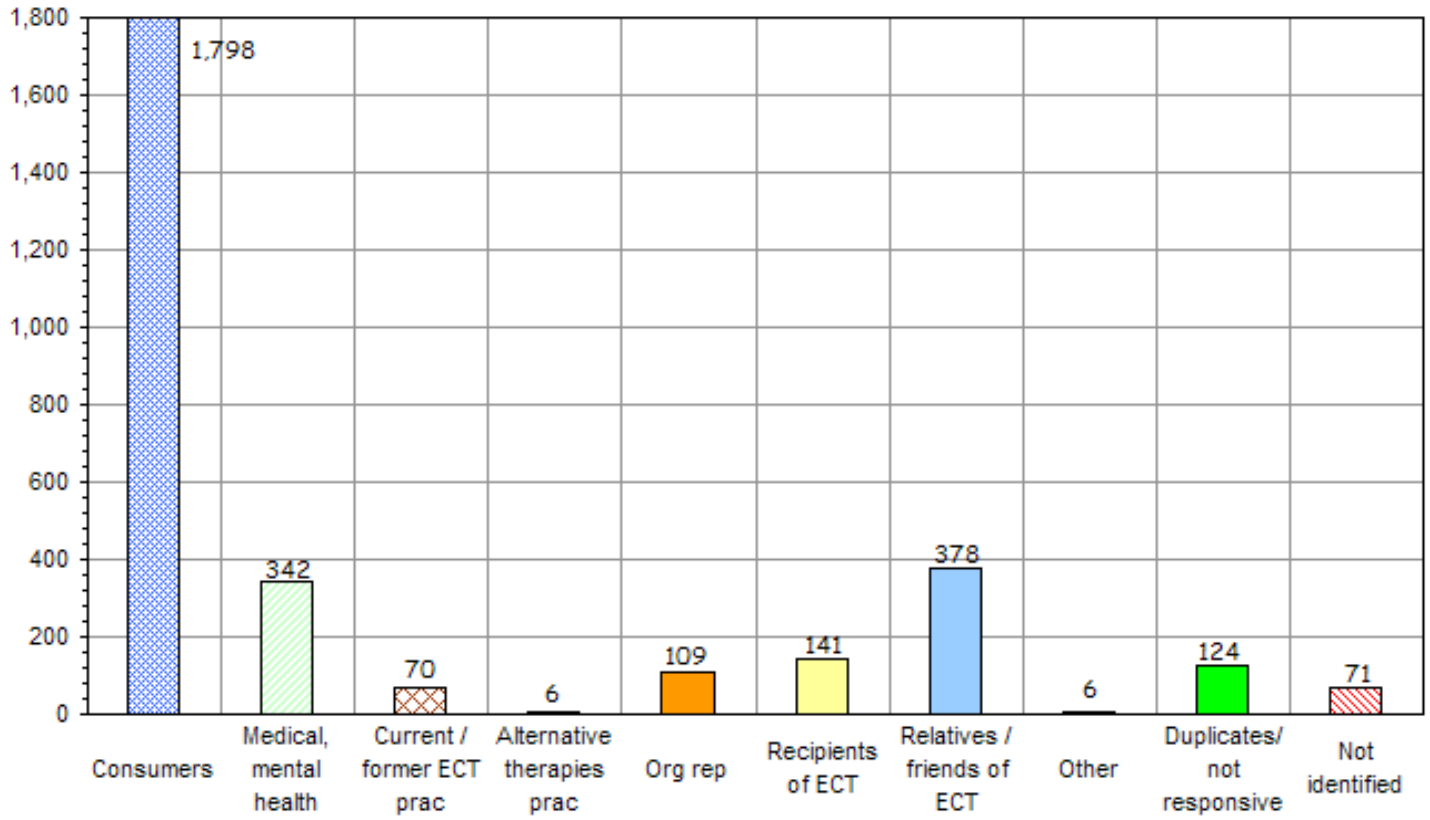
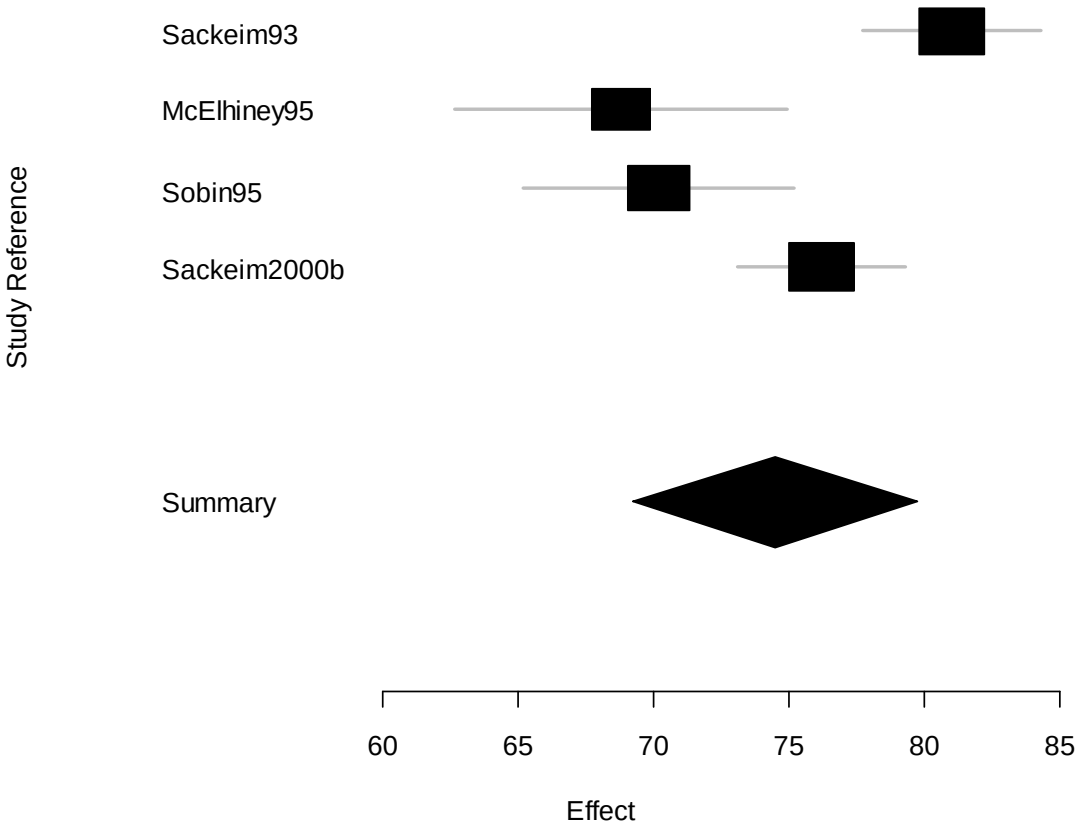


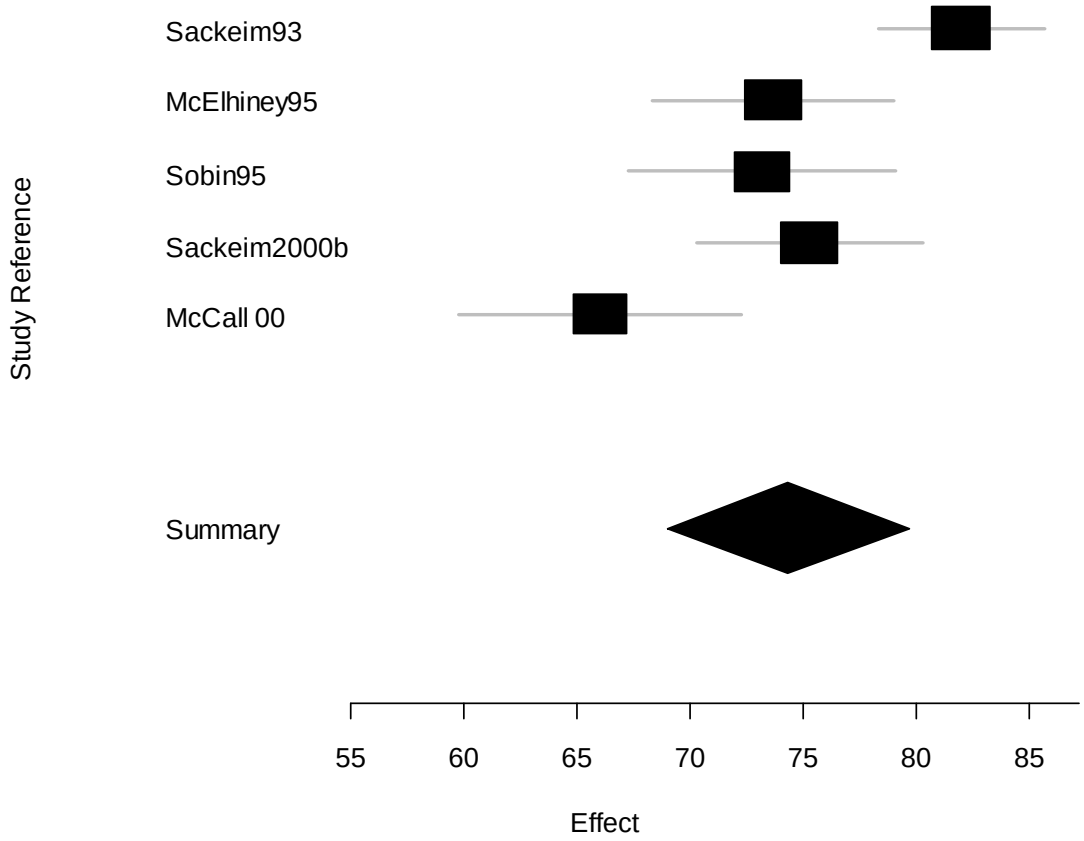
Figure 2. Meta-Analysis: Autobiographical Memory Right Unilateral Low Energy ECT (pre-post % recall)



	Effect	(lower	95%	upper)
Sackeim93	81.0	77.73		84.27
McElhiney95	68.8	62.67		74.93
Sobin95	70.2	65.20		75.20
Sackeim2000b	76.2	73.10		79.30

Summary effect: **74.49** 95%CI(69.24, 79.73)

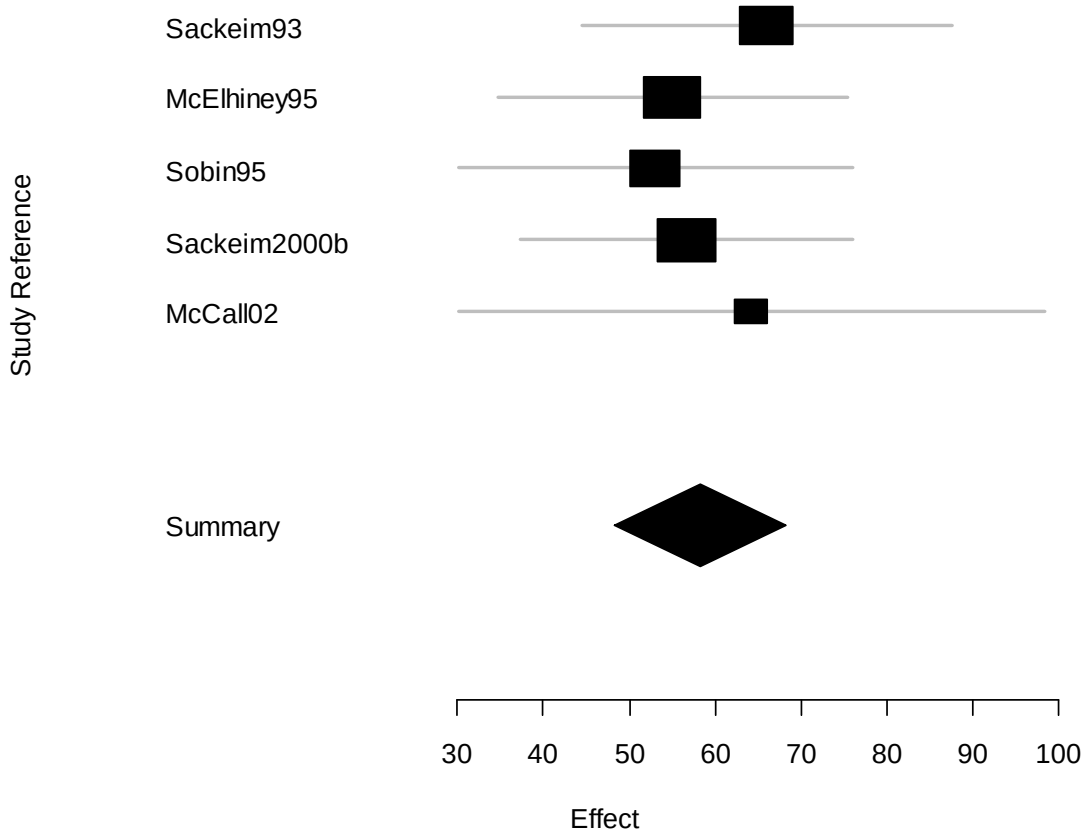
Figure 3. Meta-Analysis: Autobiographical Memory Right Unilateral Moderate Energy ECT (pre-post % recall)



	Effect	(lower	95%	upper)
Sackeim93	82.0	78.32		85.68
McElhiney95	73.7	68.33		79.07
Sobin95	73.2	67.28		79.12
Sackeim2000b	75.3	70.28		80.32
McCall 00	66.0	59.75		72.25

Summary effect: **74.35** 95%CI(69.02, 79.68)

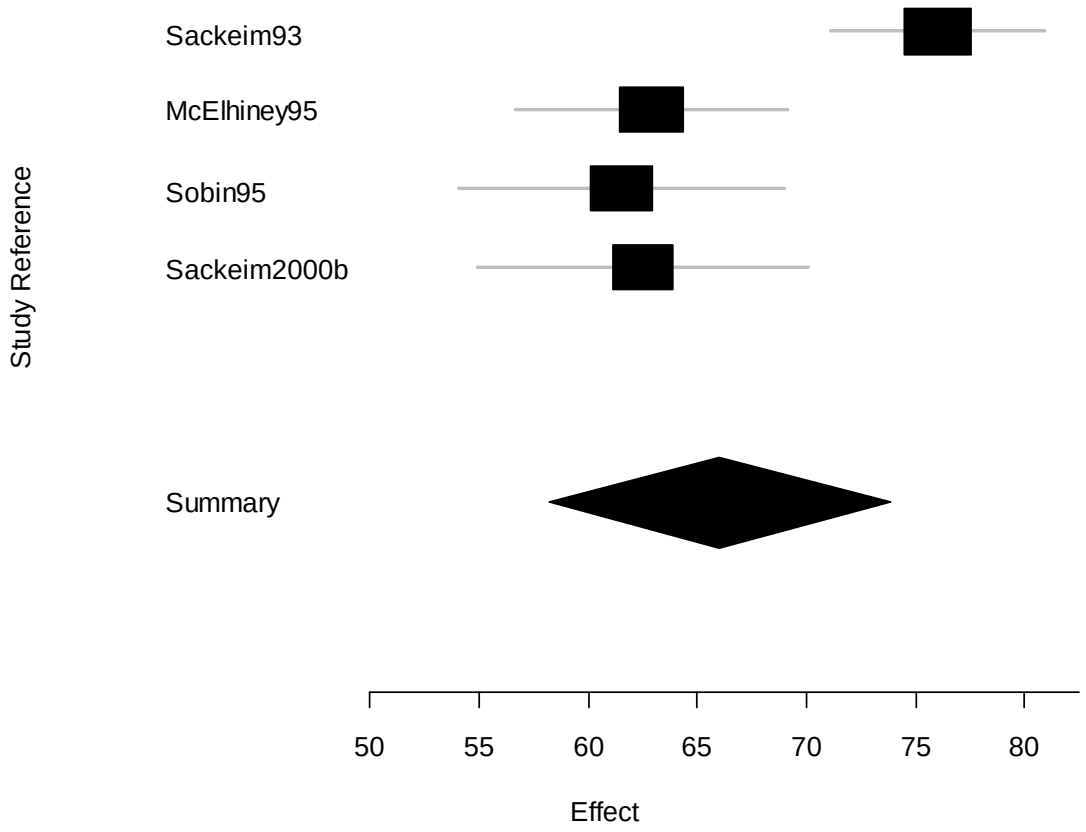
Figure 4. Meta-Analysis: Autobiographical Memory Bilateral Low Energy ECT (pre-post % recall)



	Effect	(lower	95%	upper)
Sackeim93	66.0	44.44		87.56
McElhiney95	55.0	34.62		75.38
Sobin95	53.0	30.07		75.93
Sackeim2000b	56.7	37.30		76.10
McCall02	64.2	30.10		98.30

Summary effect: **58.24** 95%CI(48.22, 68.25)

Figure 5. Meta-Analysis: Autobiographical Memory Bilateral Medium Energy ECT (pre-post % recall)



	Effect	(lower	95%	upper)
Sackeim93	76.0	71.10		80.90
McElhiney95	62.9	56.63		69.17
Sobin95	61.5	54.03		68.97
Sackeim2000b	62.5	54.90		70.10

Summary effect: **66.03** 95%CI(58.2, 73.85)

Figure 6. Time to Reorientation (minutes): Unilateral Medium vs. Bilateral Low

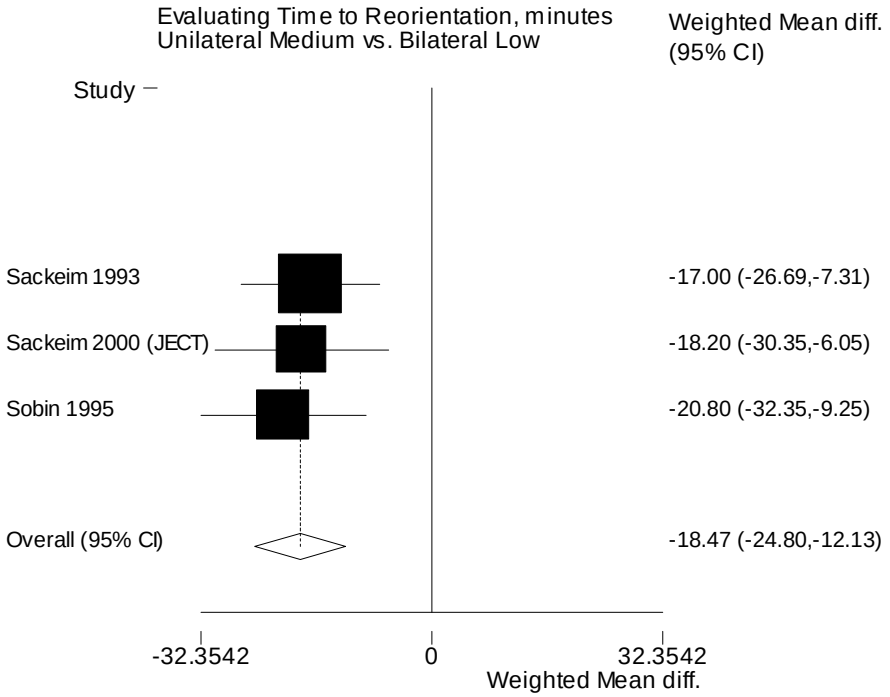


Figure 7. Time to Reorientation (minutes): Unilateral Medium vs. Bilateral High

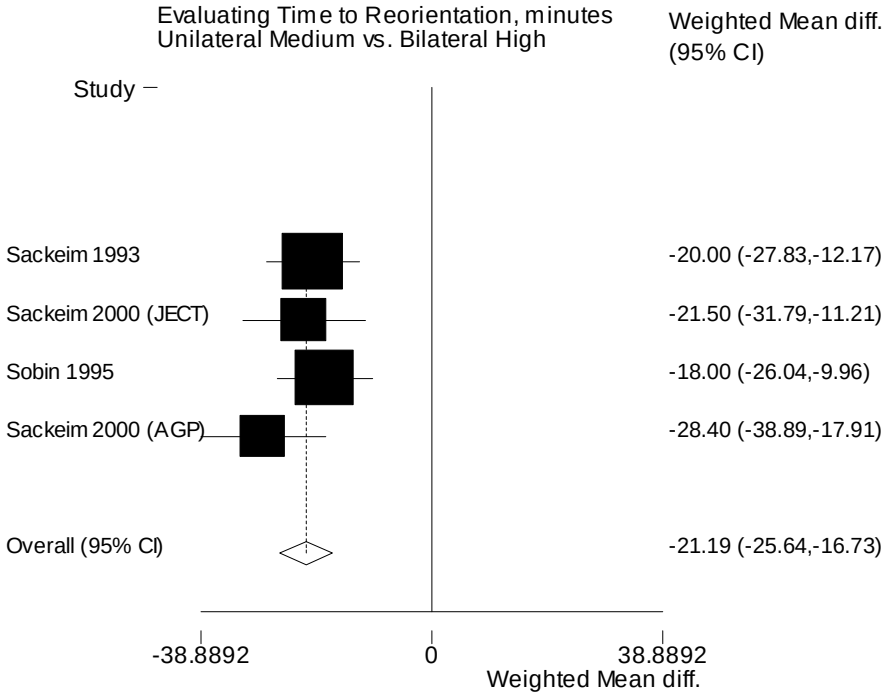


Figure 8. Time to Reorientation (minutes): Unilateral Low vs. Bilateral High

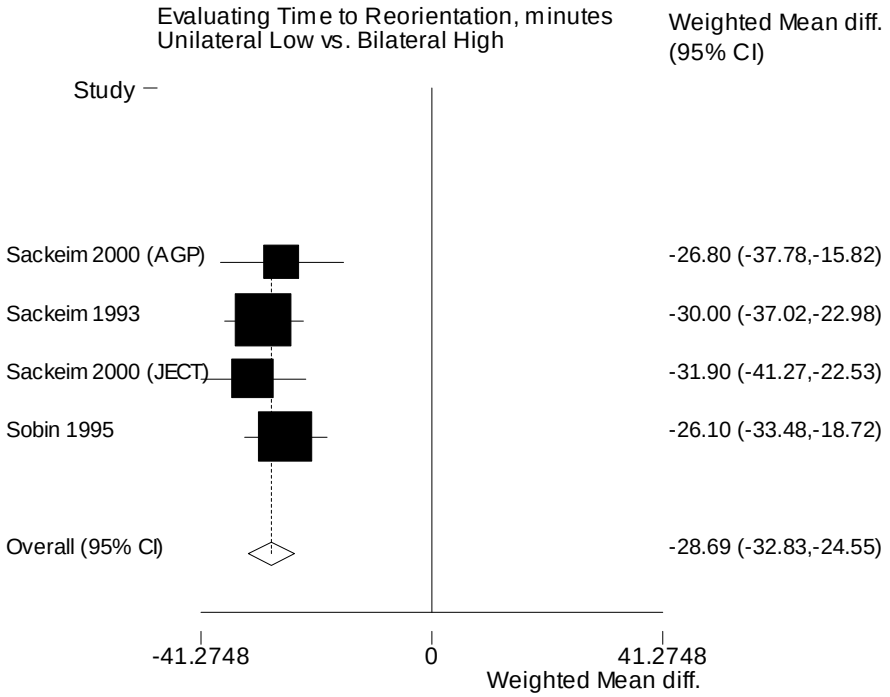


Figure 9. Time to Reorientation (minutes): Unilateral Low vs. Unilateral Medium

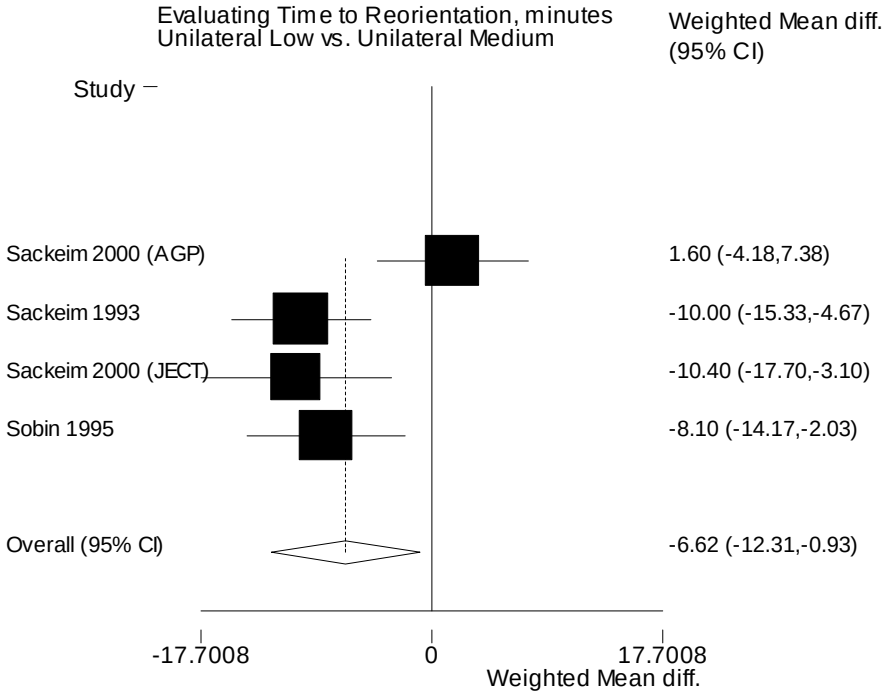


Figure 10. Time to Reorientation (minutes): Bilateral Low vs. Bilateral High

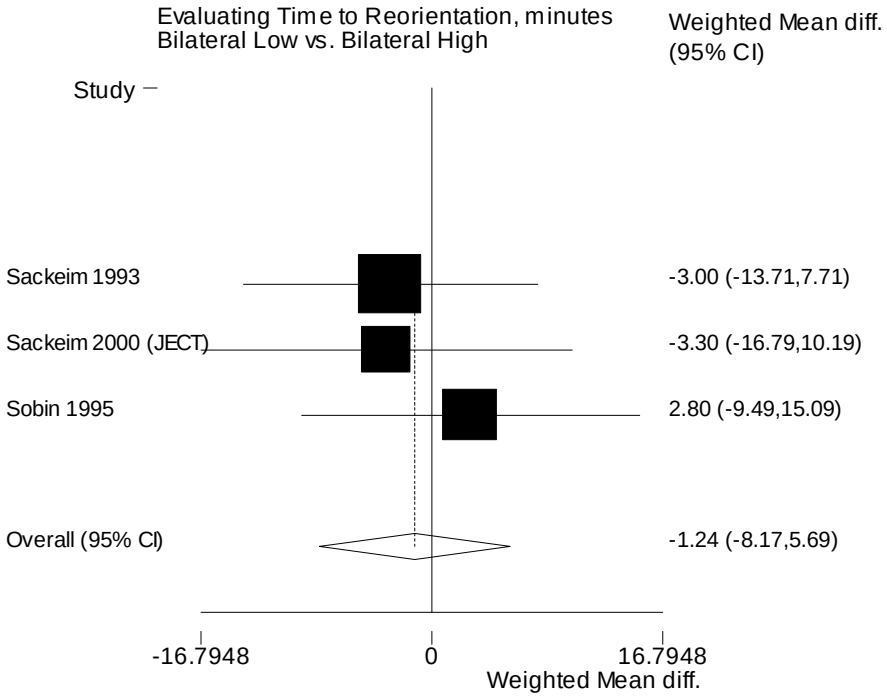


Figure 11. MMSE Immediately Post-ECT: Unilateral Medium vs. Bilateral Low

Meta-analysis: MMSE immediately post-ECT course.
Note that higher values for a group indicate worse cognitive performance. Hence, a negative value for a difference between two groups in the forest plot indicate a poorer performance in the second group.

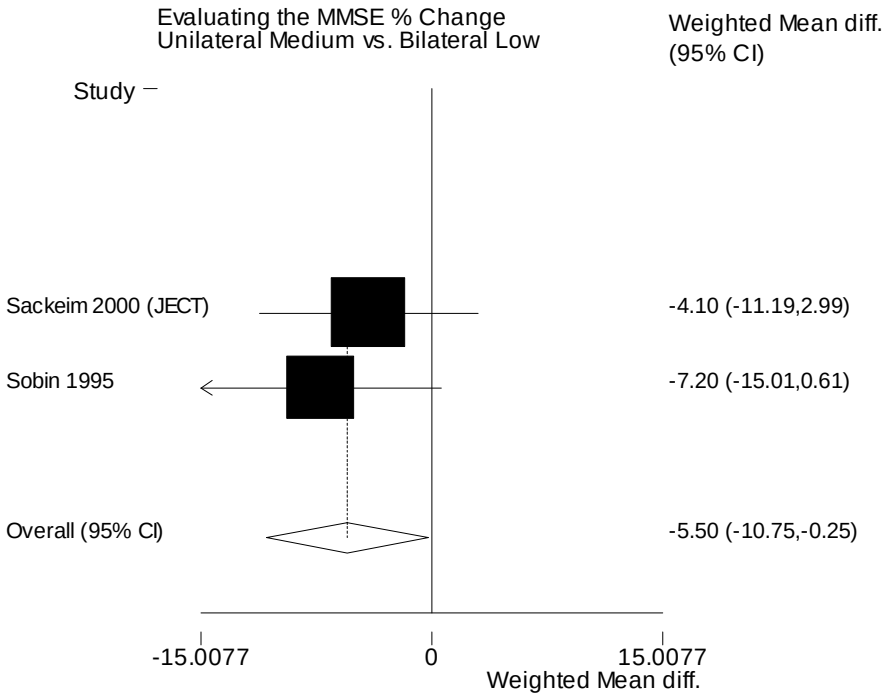


Figure 12. MMSE Immediately Post-ECT: Unilateral Medium vs. Bilateral High

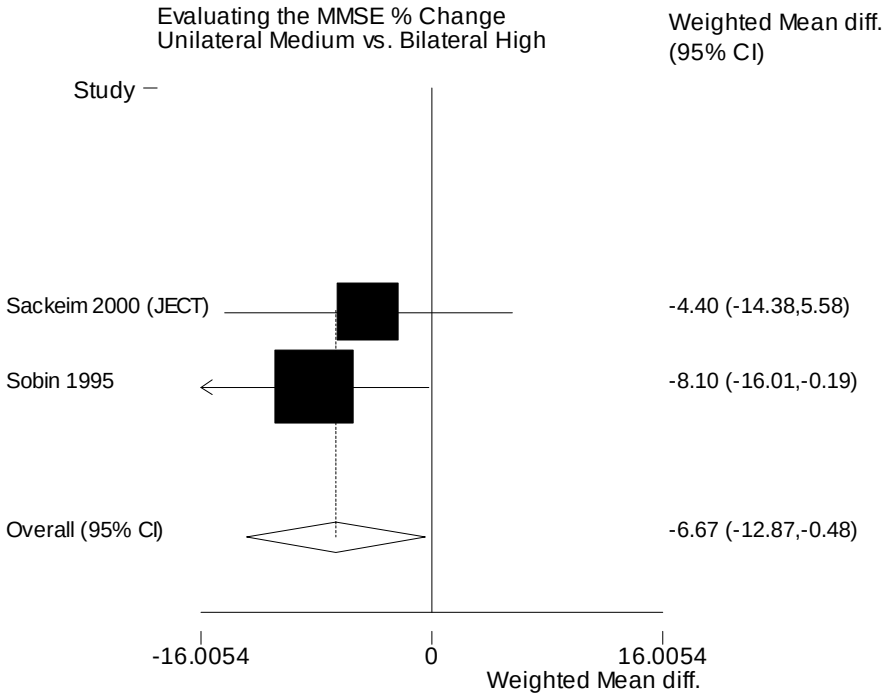


Figure 13. MMSE Immediately Post-ECT: Unilateral Low vs. Bilateral High

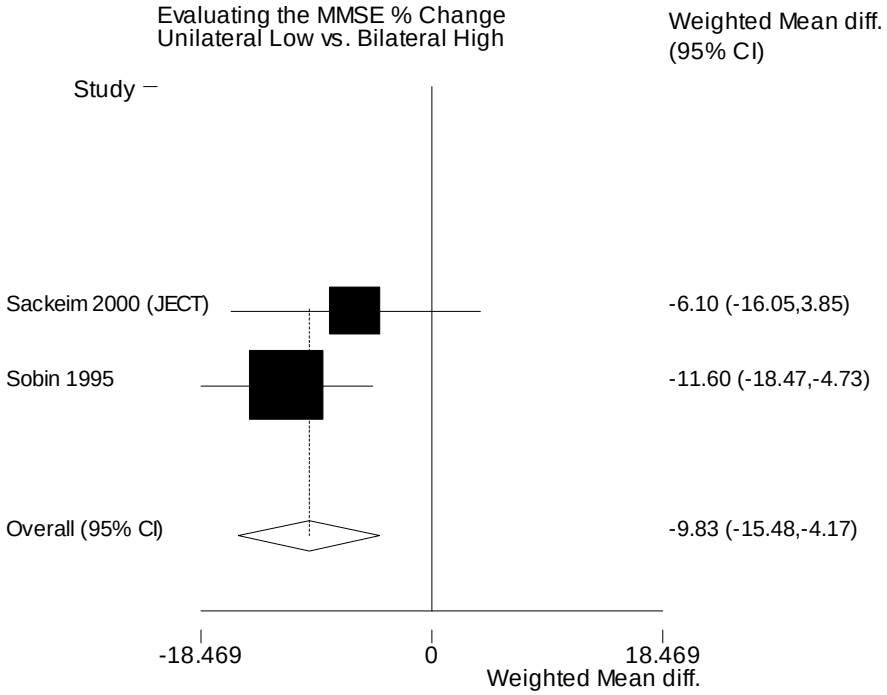


Figure 14. MMSE Immediately Post-ECT: Unilateral Low vs. Unilateral Medium

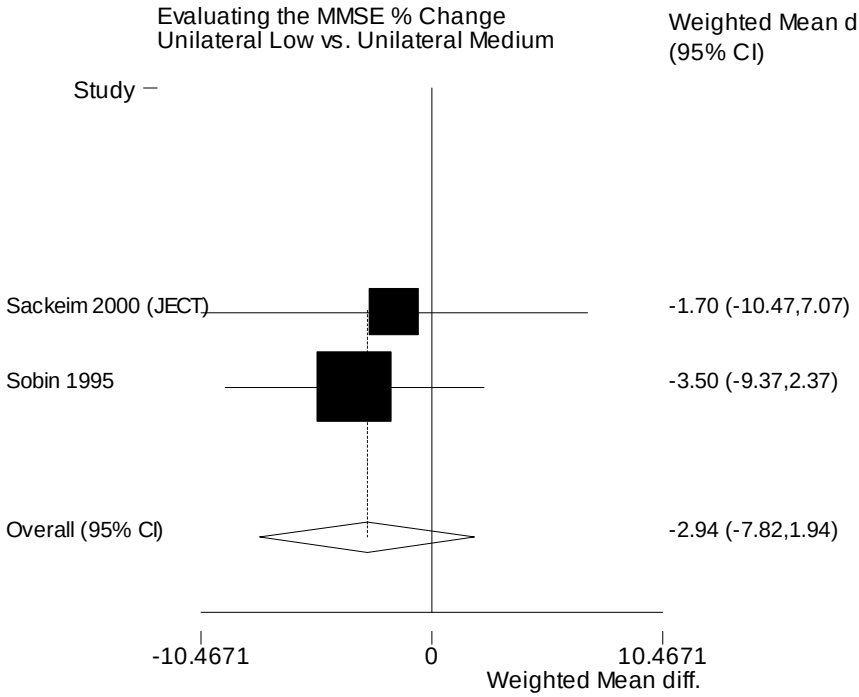


Figure 15. MMSE Immediately Post-ECT: Unilateral Low vs. Unilateral Medium

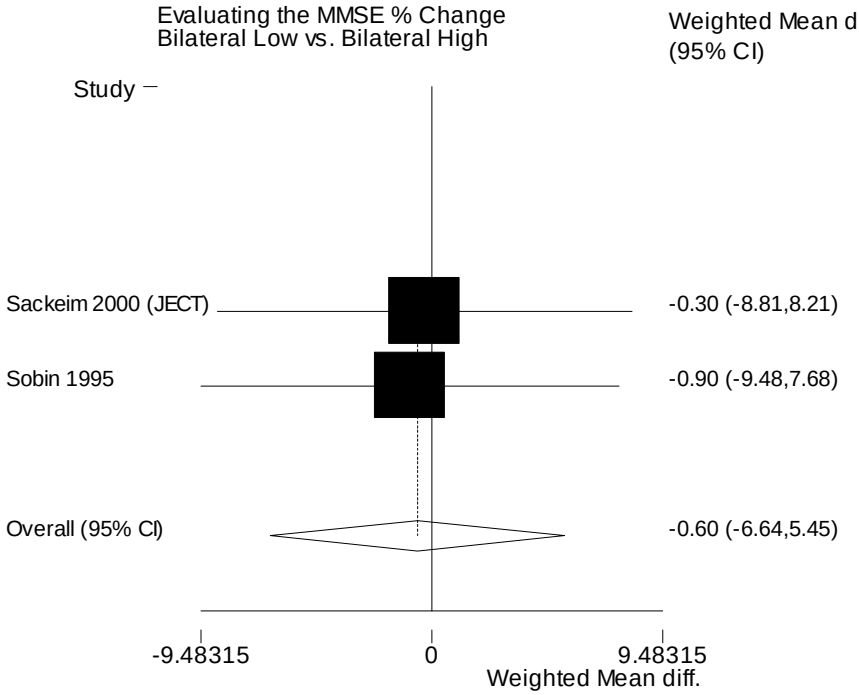


Figure 16. MMSE 2 Months Post-ECT: Unilateral Medium vs. Bilateral High

Meta-analysis MMSE at 2 months post-course

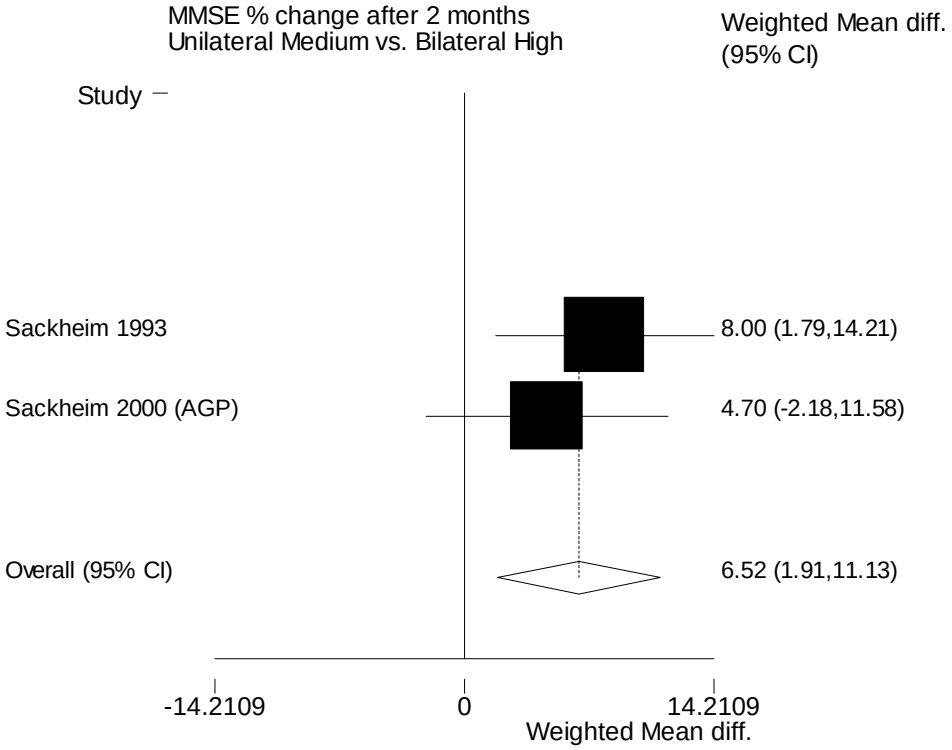


Figure 17. MMSE 2 Months Post-ECT: Unilateral Low vs. Bilateral High

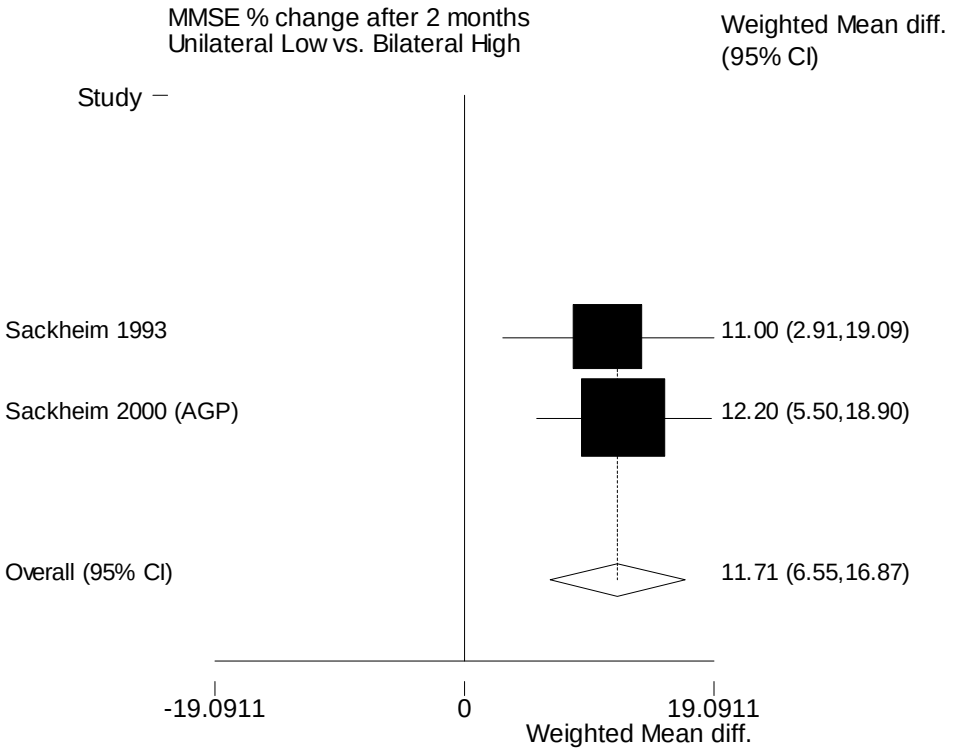


Figure 18. MMSE 2 Months Post-ECT: Unilateral Low vs Unilateral Medium

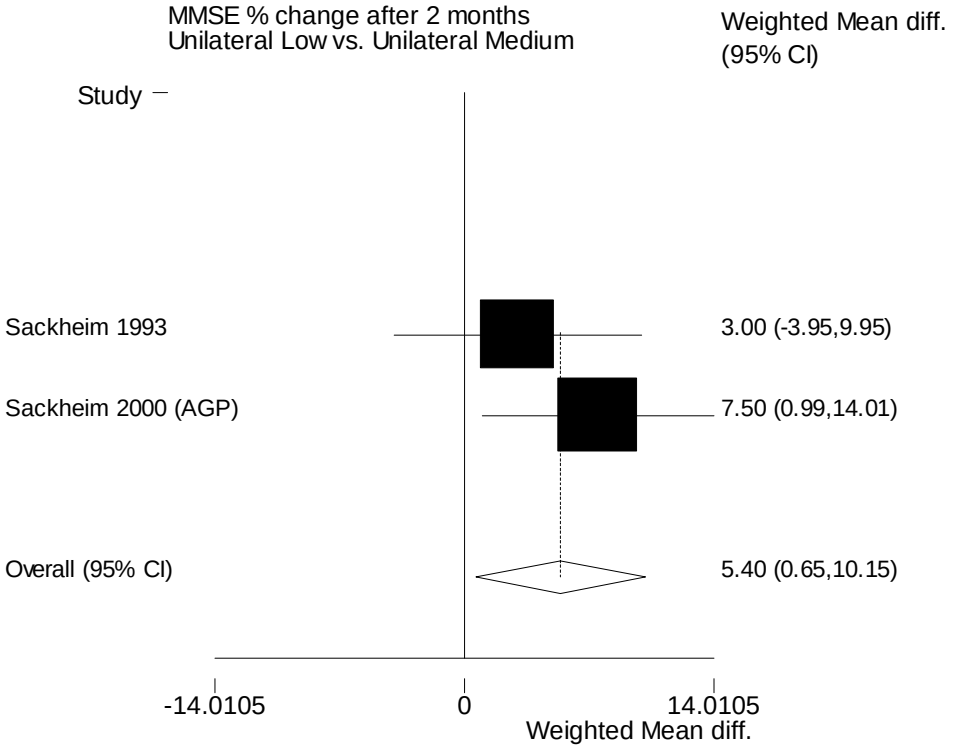


Figure 19. AMI Sub-Acute (1 Day – 1 Week): Unilateral Medium vs. Bilateral Low

Appendix: Meta-analysis: AMI; Retrograde Autobiographical Memory
Note that higher values for a group indicate worse cognitive performance. Hence, a negative value for a difference between two groups in the forest plot indicate a poorer performance in the second group.

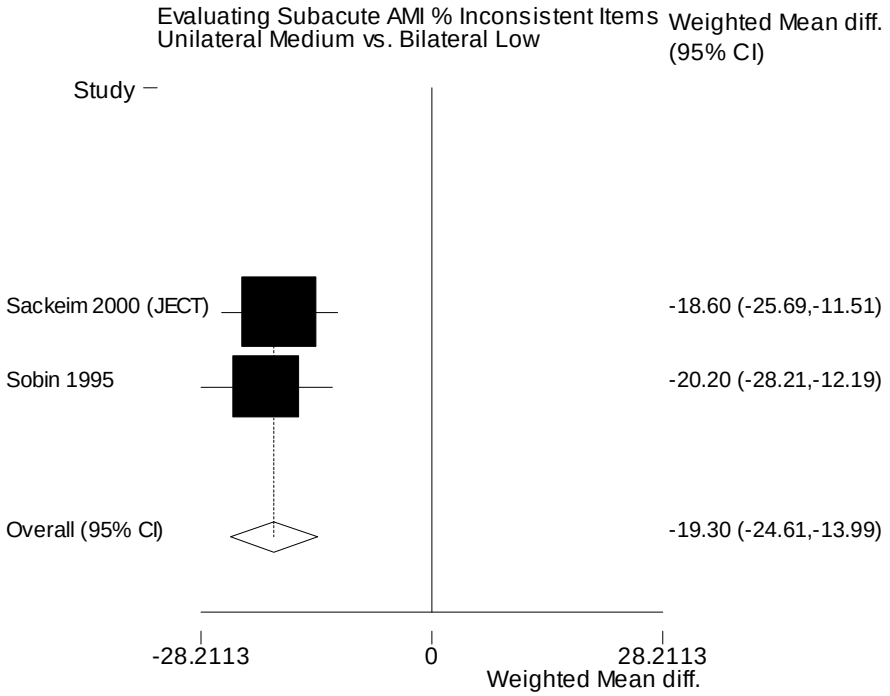


Figure 20. AMI Sub-Acute (1 Day – 1 Week): Unilateral Medium vs. Bilateral High

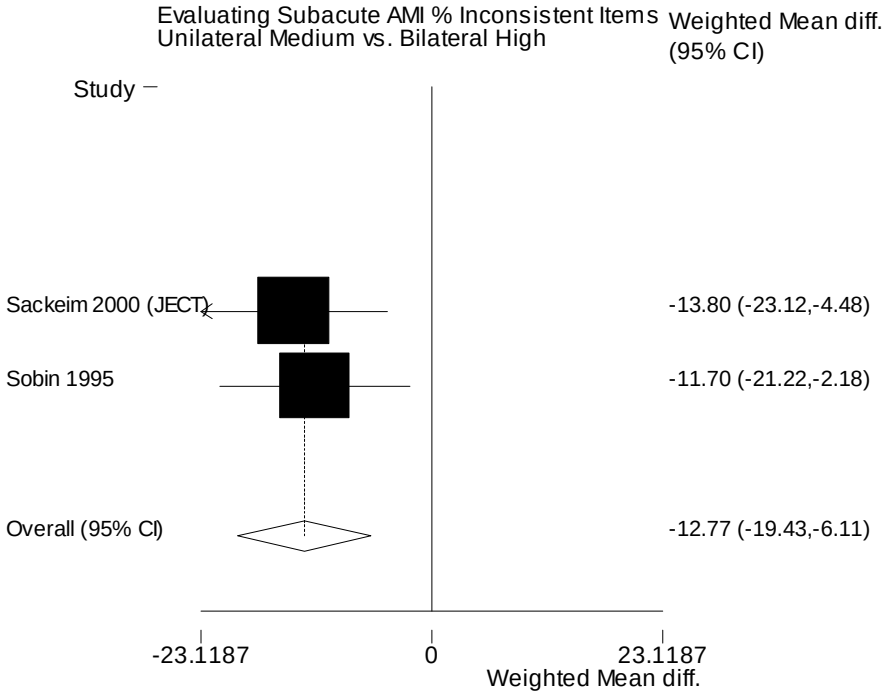


Figure 21. AMI Sub-Acute (1 Day – 1 Week): Unilateral Low vs. Bilateral High

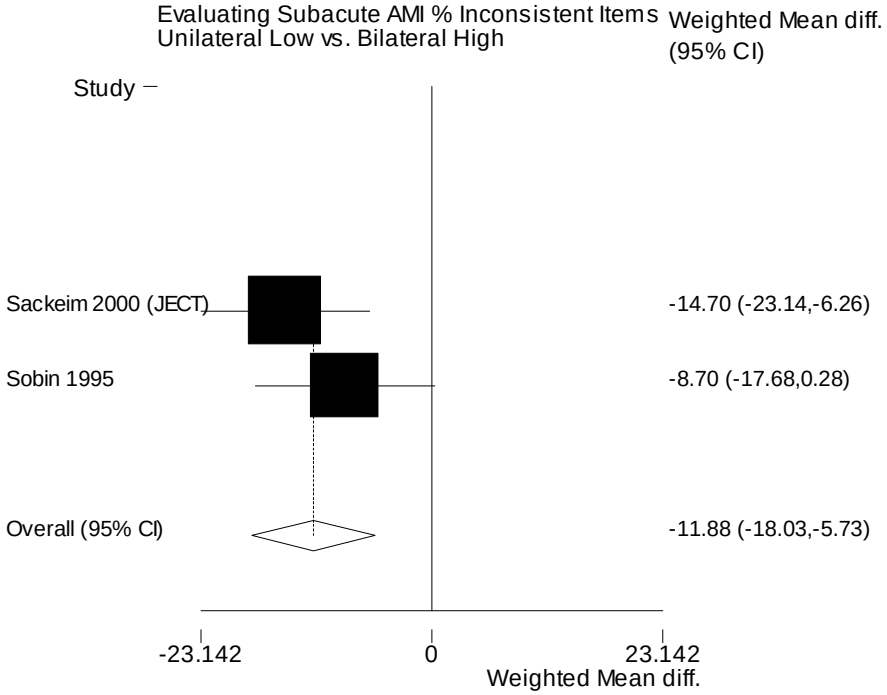


Figure 22. AMI Sub-Acute (1 Day – 1 Week): Unilateral Low vs. Unilateral Medium

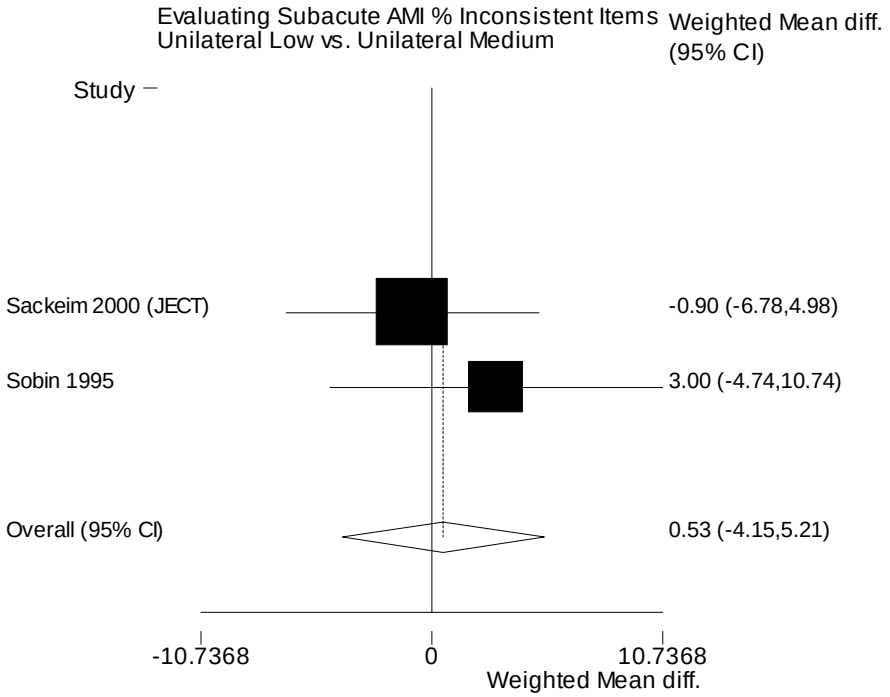


Figure 23. AMI Sub-Acute (1 Day – 1 Week): Bilateral Low vs. Bilateral High

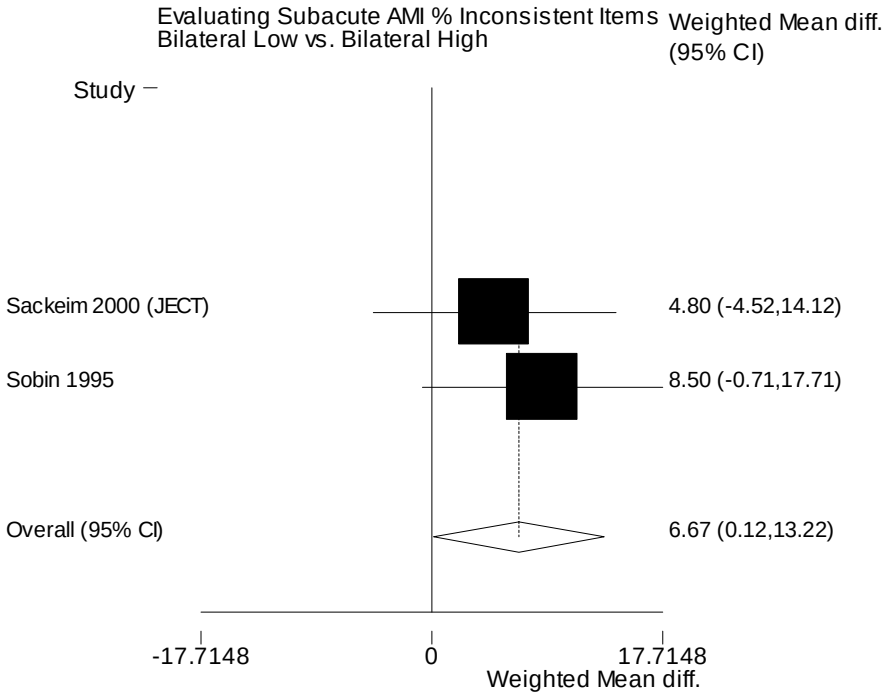


Figure 24. Depression ECT vs. Sham

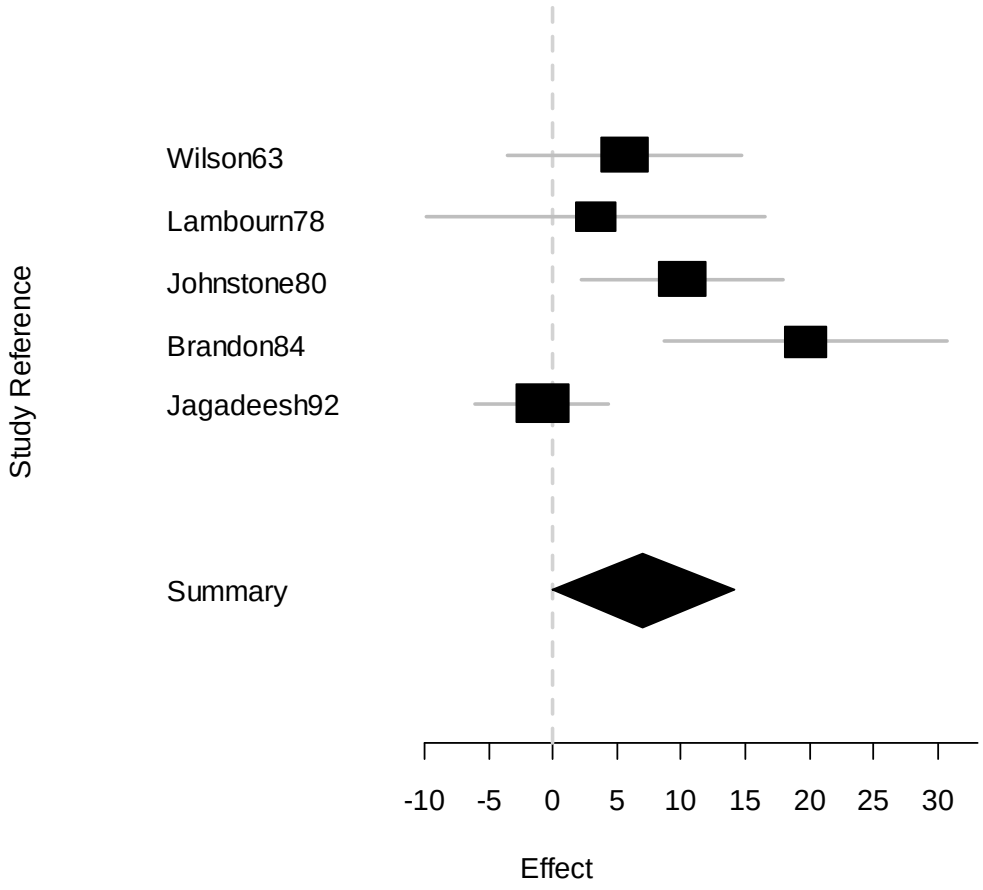


Figure 24 shows overall estimate and all study specific estimates

Figure 25. Difference in treatment effect between ECT and antidepressant medications

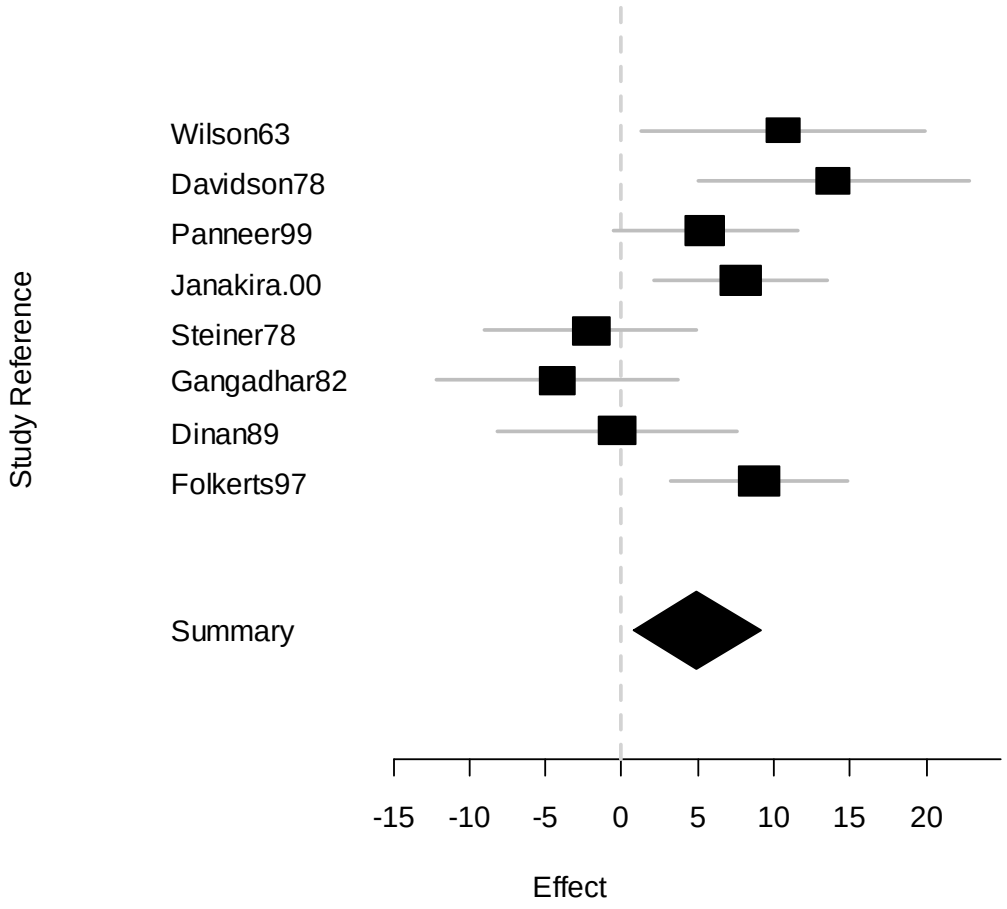


Figure 25 shows overall estimate and all study-specific estimates

Figure 26. Schizophrenia: ECT vs. Sham

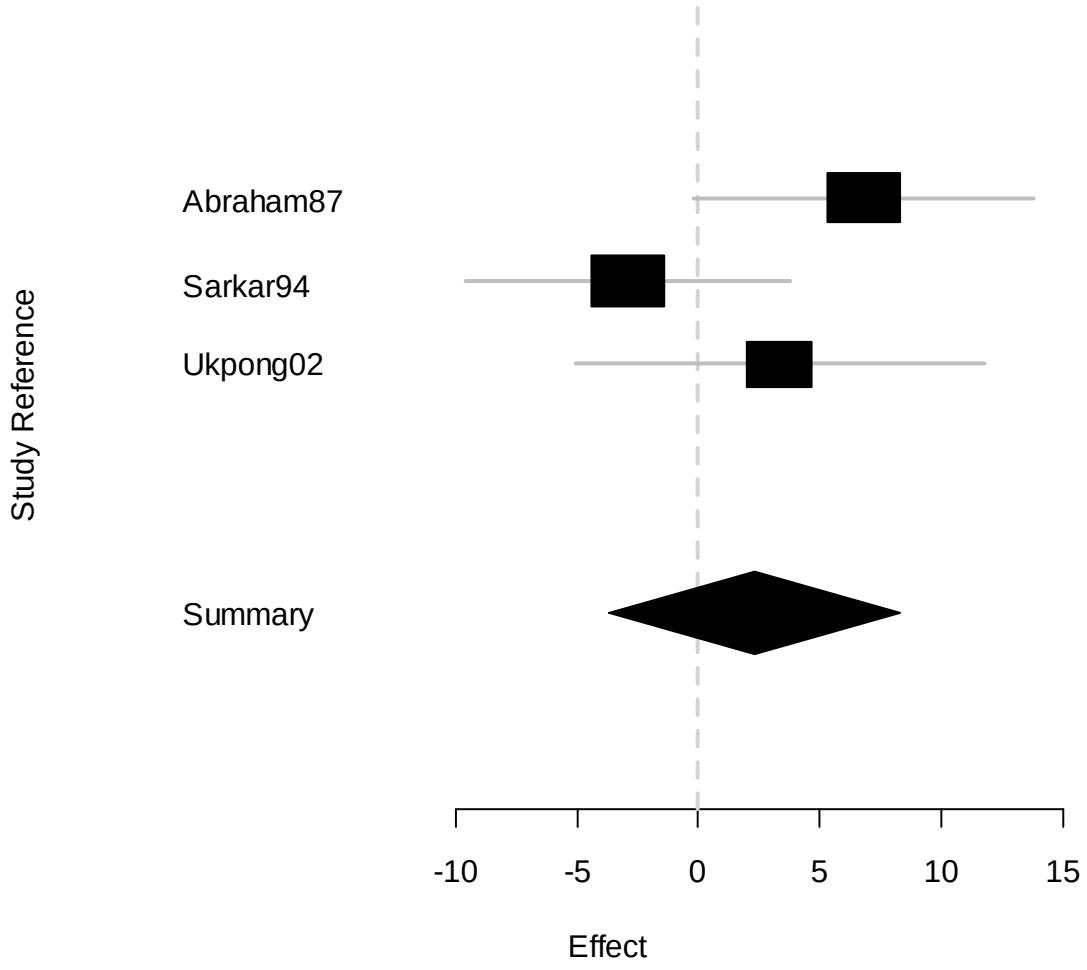


Figure 26 shows overall estimate and all study-specific estimates

Figure 27. Depression: Bilateral vs. Unilateral ECT (no dosage specified)

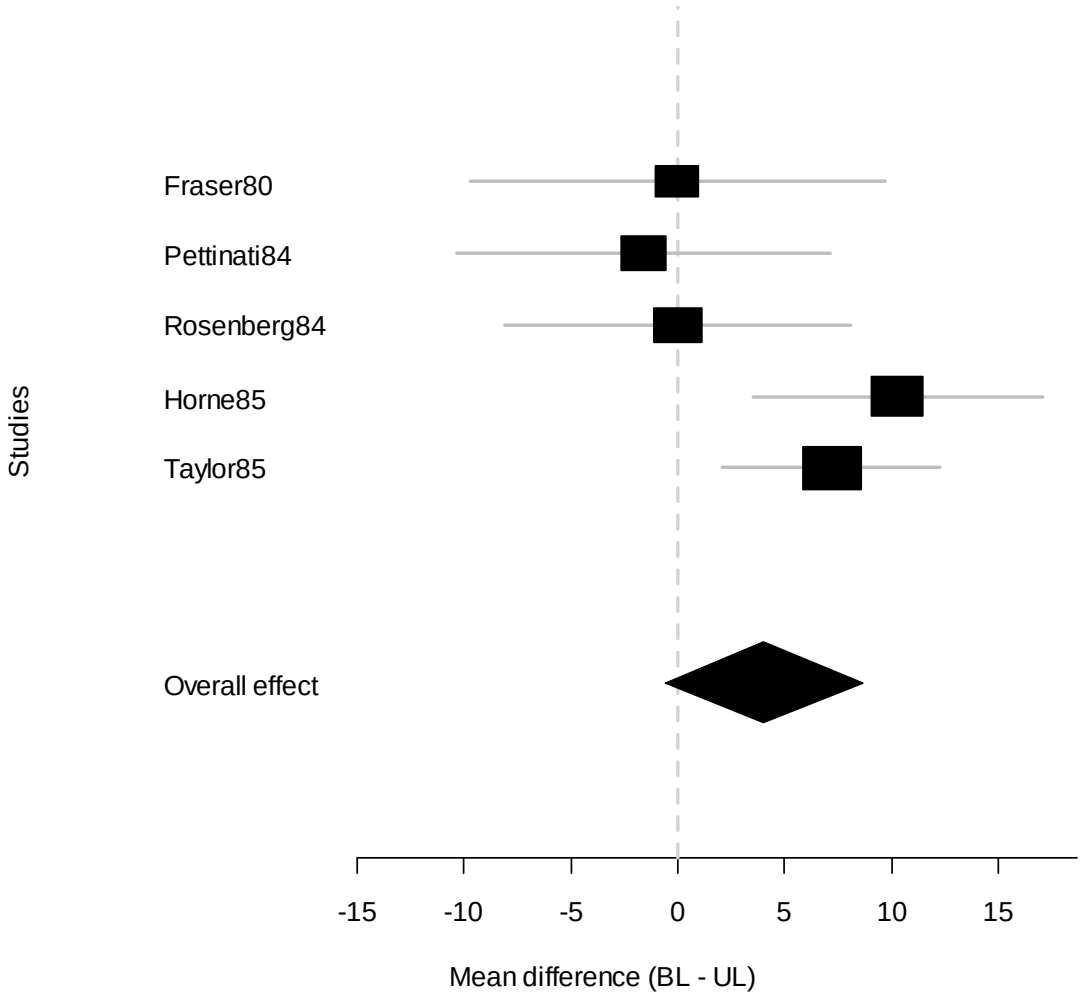


Figure 27 shows overall estimate and all study-specific estimates.

Figure 28. Depression: Bilateral (low or medium dose) vs. Unilateral ECT (high dose).

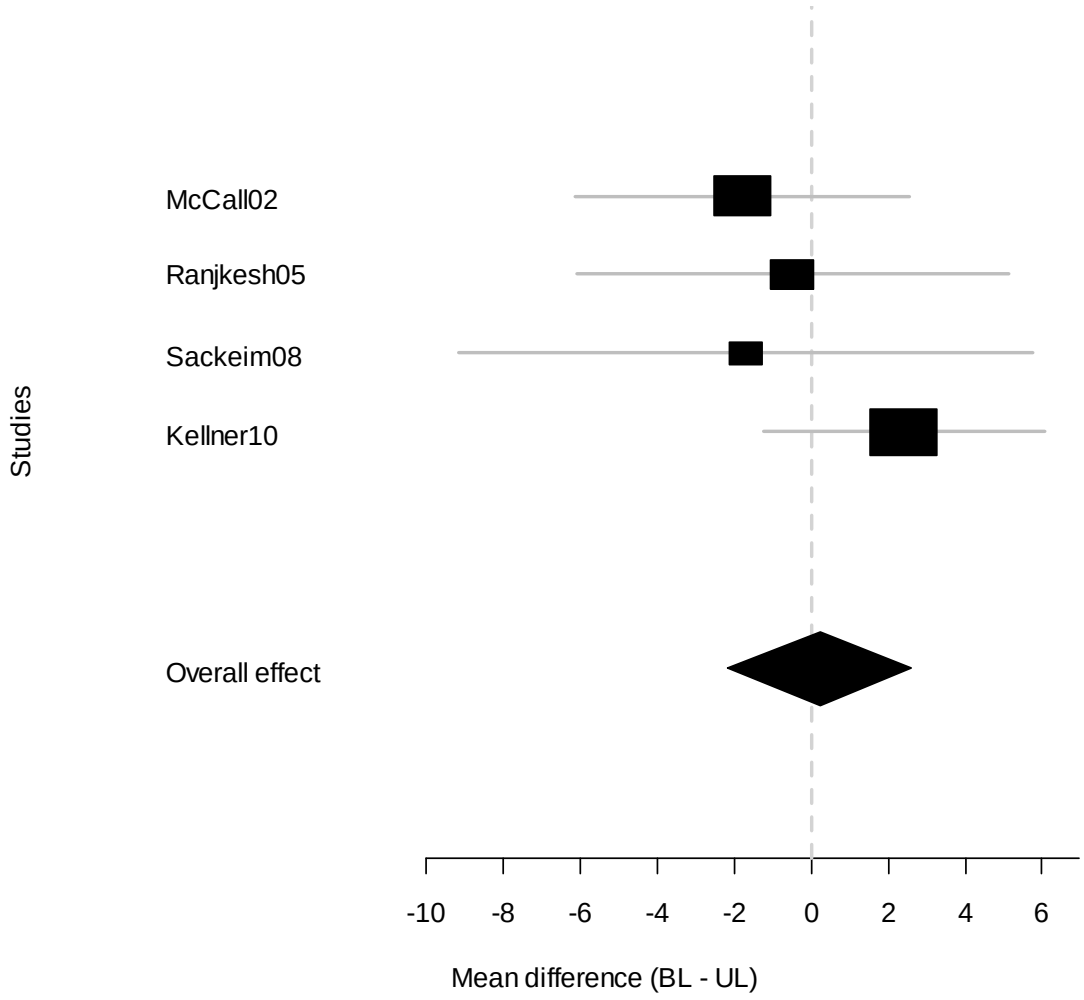


Figure 28 shows overall estimate and all study-specific estimates.

Figure 29. Depression: Frequency of Treatment (2 times vs. 3 times per week)

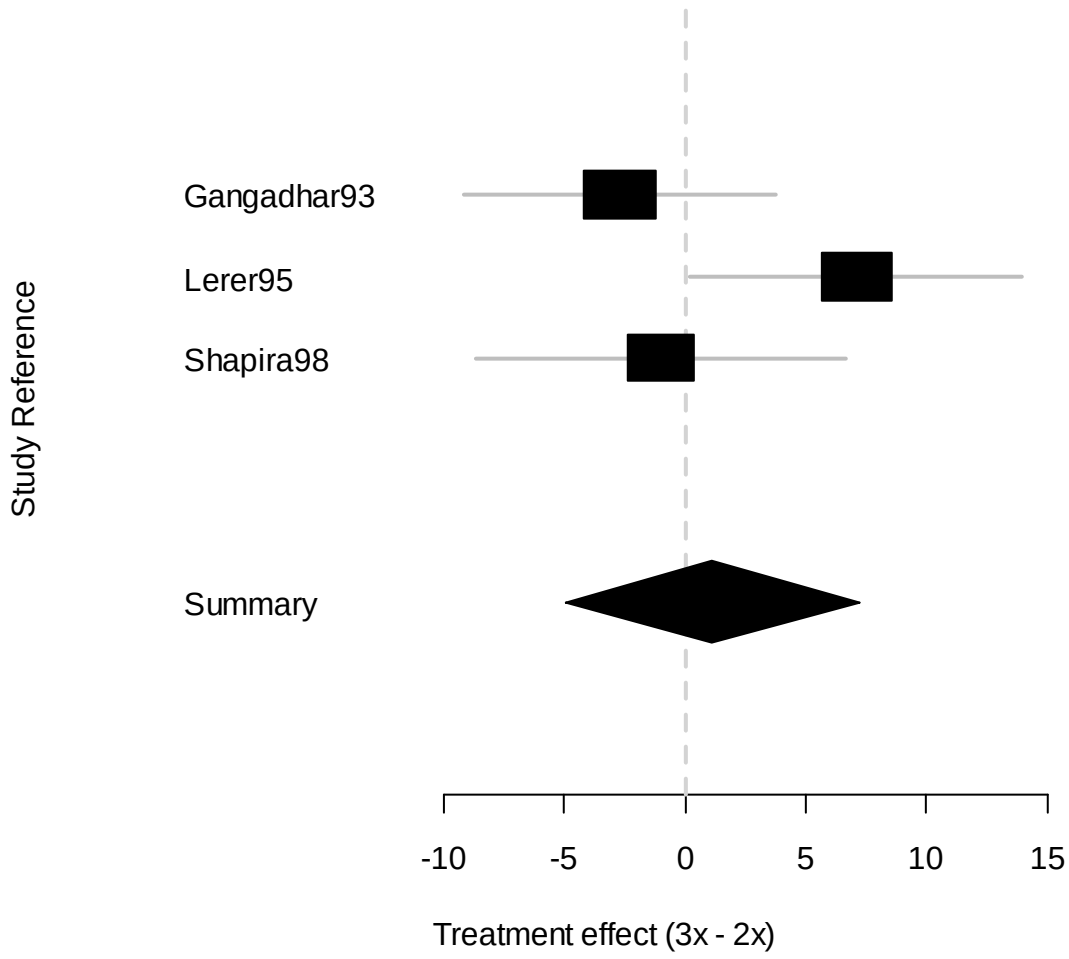


Figure 29 shows overall estimate and all study-specific estimates.

Table 8. RCTs Included in Systematic Review of Effectiveness: ECT vs. Sham for Depression

First Author	Year	Subjects	N	Comparison	Time point	Efficacy Measure	Outcome	Comment
Fink	1958	Depressive illness; SCZ	70	1. Subconvulsive ECT (27) 2. ECT BL (24) 3. Sub convulsive, then convulsive ECT (19)	Immediately Post ECT	Clinical assessment	SS: ECT better than subconvulsive	Randomized. (n=51 for group 1 v 2 comparison)
Harris	1960	Depression	12	1. ECT/placebo (4) 2. Anesthesia/placebo (4) 3. Anethesia/phenelzine (4)	Immediately Post ECT (after 2 W of treatment)	Clinical assessment	NST: ECT better than non-ECT groups	No statistical analysis reported
Fahy	1963	Depressive syndromes	60	1. ECT (20) 2. IMI(20) 3. thiopentone (20)	End of 3 W trial	Clinical assessment	NSS. Trend toward ECT and IMI more effective	Moderate severity symptoms
Wilson	1963	Depression (women)	22	1. ECT/IMI (4) 2. ECT/placebo (6) 3. Sham/IMI (6) 4. Sham/placebo (6)	Immediately Post ECT	HRSD 16	SS: ECT better than non-ECT groups	Subjects all women. Sham = anesthesia administation
McDonald	1966	Symptoms of depression	30	1. ECT (12) 2. ATI (10) 3. placebo(4) 4. sham (4)	1 M after trial initiation, approximately 1 W post ECT	MMPI depression; clinical assessment	SS: ECT v control (combined placebo and sham)	
Lambourn	1978	Depressive psychosis	32	1. ECT 2. Sham	1 D 1 M	HRSD	NSS:ECT and Sham	Constrained randomization, gender and age matched: ECT was UL BP low energy. 6 treatments.
Johnstone	1980	Severe endogenous depression	70	1. ECT 2. Sham	1 W 1 M 6 M	HRSD	SS: Real better than sham post-course (weekly assessment) NSS: at 1 M and 6 M follow up.	62 completed. ECT treatment twice per week for 4 weeks
West	1981	Depressive illness	22	1. ECT (11) 2. Sham (11)	5 D	BDI Clinical assessments VAS	SS: ECT vs. sham, and ECT change from baseline	ECT treatment twice per week for 3weeks. After 6 treatments, crossover if clinically determined
Brandon	1984	Depression with retardation, delusions, "neurotic"	95	1. ECT (53) 2. Sham (42)	Mid course (2 w) Post course 8 W 24 W	HRSD	SS: 2 W (mid course) and post course NSS: 8 W and 24 W	ECT treatment twice per week for 4 weeks: At 8 W, sham seemed to improve, ECT group did not worsen.

Gregory	1985	Depressive illness	69	1. ECT BT 2. ECT RUL 3. Sham	Post 1 M 3 M 6 M	MADRS, HRSD	SS: ECT (BL and RUL) v sham post course. NSS: 1 M, 3 M, 6 M	44 completed . BL and RUL combined: ECT v sham. BL better than UL better than sham post.
Jagadeesh	1992	MDD endogenous subtype (RDC)	24	1. ECT x 6 (12) 2. 1 real ECT, then 5 sham (12)	1 D	HRSD 16 (no weight loss item), global rating scale, Newcastle prognostic	NSS: between groups	Sham group received 1 real ECT to start, followed by sham treatment.

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
D: day
H: hour
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
SS: statistically significant
RDC: research diagnostic criteria
RUL: right unilateral
VAS: visual analogue scale
W: week

Table 9. RCTs Included in Systematic Review of Effectiveness: ECT vs. Placebo for Depression

First Author	Year	Subjects	N	Comparison	Time point	Efficacy Measure	Outcome	Comment
Wittenborn	1962	Depression	63	1. ECT (21) 2. Placebo(21) 3. IMI (21)	Post treatment	WPRS, MMPI psychasthenia, depression,,Clyde mood scale	SS: IMI better than ECT. NSS: ECT not better than IMI or placebo.	Continuous analysis. No SD.
Wilson	1963	Depression (women)	22	1. ECT/IMI (4) 2. ECT/placebo (6) 3. Sham/IMI (6) 4. Sham/placebo (6)	Post (1 W)	HRSD	SS: ECT better than non-ECT groups	ECT placebo best, then ECT IMI, IMI placebo least effective
Greenblatt	1964	Depressive illness	281	1. ECT (63) 2. IMI (73) 3. Phenelzine (38) 4. Marplan (68) 5. Placebo (39)	Post treatment	Clinical assessment	SS: ECT better than other groups	ECT better than placebo or meds
MRC/ Shepherd	1965	Depressive illness	250	1. ECT (65) 2. Placebo (61) 3. IMI (63) 4. Phenelzine (61)	4 W after initiation of treatment, 6 M	Clinical assessment	SS: 4w ECT and IMI better than placebo 6 m : ECT and IMI better than placebo	ECT 4-8 treatments in first 3.5 W. IMI better in men, ECT better in women
McDonald	1966	Symptoms of depression	30	1. ECT (12) 2. ATI (10) 3. placebo(4) 4. sham (4)	1 M after trial initiation, approximately 1 W post ECT	MMPI depression, psychasthenia, clinical MD RN rating	SS: ECT v control (combined placebo and sham)	ECT and ATI better than placebo/sham
Abou-Saleh	1995	MDD (DSM-III)	48	1. ECT (25) 2. antidepressant (10) 3. placebo (12) 4. normal control (26)	Post	HRSD	SS: ECT better than placebo	Also 26 normal controls. Also examined neopterins, biopterins.

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
D: day
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
SS: statistically significant
RDC: research diagnostic criteria
RUL: right unilateral
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 10. RCTs Included in Systematic Review of Effectiveness: ECT vs. Antidepressants for Depression

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Bruce	1960	41	Depression-endogenous	1. ECT (22) 2. IMI (19)	1 M after initiation of trial	Clinical assessment	NSS	Categorical analysis
Harris	1960	12	Depressive reaction	1. ECT/placebo (4) 2. Sham/placebo (4) 3. Sham/phenelzine (4)	2 W after initiation of trial	Clinical assessment	NST	All women subjects
Robin	1962	26	Depression	1. ECT/placebo (14) 2. Anes (sham)/IMI (12)	1 M after initiation of trial	Clinical ratings, HRSD, Behavior ratings	SS: ECT better than IMI	Categorical analysis
Hutchinson	1963	200	Depression	1. ECT 2. IMI 3.Tranylcypromine/trifluoperazine 4.ATI 5. Pheniparzine 6. Phenelzine 7. Chlorprothixene	3 W post initiation of trial	Scale of depressive symptoms	SS: ECT better than all meds.	All female subjects. Adequate doses. No SD.
Wilson	1963	22	Depression: bipolar and unipolar, No schizoaffective	1. ECT/imi (4) 2. ECT/placebo (6) 3. Sham/imi (6) 4.Sham/placebo (6)	4 - 5 W post initiation of trial	HRSD 16, MMPI depression	SS: ECT placebo best, ECT IMI next, IMI placebo least effective.	All women subjects. Dichotomous, continuous analyses, +SD
MRC/ Shepherd	1965	250	Depressive illness	1. ECT (65) 2. Placebo (61) 3. IMI (63) 4. Phenelzine (61)	4 W 6 M	Clinical assessment	SS: At 4 W, 6 M, IMI and ECT better than placebo	IMI better in men, ECT better in women
McDonald	1966	30	Symptoms of depression	1. ECT (12) 2. ATI (10) 3. placebo(4) 4. sham (4)	1 M after trial initiation, approximately 1 W post ECT	Clinical rating DRS, MMPI depression, psychasthenia	Continuous SS: ECT and ATI better than placebo/sham. NSS: ECT and ATI	
Fahy	1963	60	Depressive syndromes	1. ECT (thiopentone anesthesia) (17) 2. IMI (16) 3. thiopentone (intended as sham) (17)	End of 3 W trial	Clinical assessment	NSS. Trend toward ECT and IMI more effective	ECT: 2x/W x 3 W. Blinded only for rater. Moderate severity symptoms.

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Wittenborn	1962	63	Non psychotic neurotic depression	1. ECT (21) 2. Placebo(21) 3. IMI (21)	Post treatment	WPRS, MMPI psychasthenia, depression, Clyde mood scale	SS: IMI better than ECT. NSS: ECT not better than IMI or placebo	No SD. All women subjects.
Greenblatt	1964	281	Depression mixed dx, none >50%	1. ECT (63) 2. IMI (73) 3. Phenelzine (38) 4. Marplan (68) 5. Placebo (39)	Post (8 W p initiation)	Clinician global rating, DRS (dep rating scale)	SS: ECT better than placebo or meds	Not blinded for ECT
Davidson	1978	17	Refractory depression (primary, secondary to anxiety, character disorder)	1. ECT (9) 2. ATI/phenelzine (8)	Post treatment	HRSD, BDI, STAI	NST	
Steiner	1978	12	Depression	1. ECT (4) 2. IMI/placebo (4) 3. IMI/T3 (4)	Post (5 W p initiation)	HRSD, CGI	Continous Dichotomous NSS.	All women subjects. Individual HRSD data.
Gangadhar	1982	32	Endogenous depression	1. ECT/placebo (11) 2. IMI/sham (13)	4, 6, 8, 12, 24 W	HRSD	NSS all comparisons.	ECT 4 wk trial + mECT. Both groups maintained improvement to 24 M.
Dinan	1989	30	Major depression-tricyclic nonresponders	1. TCA/ECT 2. TCA/lithium	3 W	HRSD	NSS	Both groups improved. Lithium responded more rapidly with more mental state , changed by 7 D.
Folkerts	1997	39	Major depression ATHF ≥2	1. ECT 2. paroxetine	0-1 W (3W p initiation)	HRSD	SS: ECT better than paroxetine, significant difference after W 1.	Crossover after 3rd W. Data out to 6W.
Paneer Selvan	1999	28	MDD, treatment naïve	1. ECT BL (14) 2. IMI (14)	4 W	HRSD17, MADRS, BDI, VAS, CGI	NSS: between groups. SS: change from baseline both groups	Treatment naïve. BL ECT twice per week x 4 W (max 8 ECTs)
Janakiramaiah	2000	45	Melancholic depressives	1. ECT (15) 2. IMI (15) 3. yoga (15)	4 W	BDI, HRSD	SS: ECT better than yoga. NSS: Yoga and IMI. NST: ECT, IMI	

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Abou-Saleh	1995	48	MDD (DSM-III)	1. ECT (25) 2. antidepressant (10) 3. placebo (12) 4. normal control (26)	Post treatment	HRSD	SS: ECT better than placebo	26 normal controls did not receive ECT. Also examined neopterins, biopterins.
Greenblatt	1962	128	Depression mixed none >50%	1. ECT (28) 2. IMI (37) 3. Phenelzine (30) 4. Isocarboxyzid (33)	8 W after starting trial	Clinical assessment, DRS	SS: ECT more marked recoveries than meds	Not included in systematic review; same dataset as Greenblatt 1964.

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
D: day
DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant
T3: tri-iodothyroxine
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 11. RCTs Included in Systematic Review of Effectiveness: Electrode Placement by Energy Dose for Depression

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Fraser	1980	29	Depressive illness, geriatric	ULND BL	1 D 3 W	HRSD	NSS: UL = BL at either time point	
Weiner	1986	53	MDD, RDC	Pulse UL Sine UL Pulse BL Sine BL	6 M	HRSD Zung self rating depression scale	NSS: all groups SS: baseline change in ECT groups	21 controls who received no ECT
Janicak	1991	27	Depressed	ULND BL	3-5 D 6 M	HRSD24	NSS: between groups SS: improvement from baseline at both time points	
Sackeim	2000	80	MDD, RDC	RUL 1.5ST RUL 2.5ST RUL 6ST BL 2.5ST	1-2 D 1 W	HRSD CGI	SS: BL and RUL hi better than RUL moderate or low energy	RUL high energy is as effective as BL, less cognitive effects
Sackeim	2008	90	MDE, RDC DSMIV	RUL 6ST BP RUL 6ST UBP BL 2.5ST BP BL 2.5ST UBP	2 D 1 W	HRSD BDI, CGI	SS: UBP BL worse than other 3 groups.	Ungraph
McCall	2000	72	MDE DSM IIIR	RUL 2.25ST RUL fixed hi	1-2 D	HRSD21	SS: high dose RUL better than moderate dose NST: change from baseline	
Heikman	2002	24	MDE	RUL 5ST RUL 2.5 ST BF ST	1-3 D	HRSD 17	SS: high dose RUL faster response than low dose BF. NSS: trend toward higher response with high dose RUL	
McCall	2002	77	MDE	RUL 8ST (40) BL 1.5ST (37)	1-3 D 2 W 4 W	HRSD21 BDI	NSS: RUL 8ST not different then BL1.5 ST NST: but appears to be some improvement from baseline, then relapse	
Eschweiler	2007	92	Pharmacoresistant major depression	BF RUL	1 D	HRSD21	NSS: between groups difference	
Kimball	2009	66	MDE, DSMIIIR	Moderate titrated RUL Fixed high dose RUL	1-2 D	HRSD21	NSS: between groups difference	

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Kellner	2010	230	Bipolar and unipolar depression	BF 1.5ST BT 1.5 ST (72) RUL 6ST (77)	24-36 H	HRSD24	SS: All 3 groups had improvement from baseline. BT more rapid response	Remission categorical data as well
Taylor	1985	37	Melancholia (DSM-III)	BL (15) RUL (22)	48-73 H	HRSD15	Both demonstrate significant clinical improvement. SS: BL better	
Levy	1968	40	Depression	UL BL	6 H	Cronholm Ottosson	NSS trend for BL	35 J for all treatments
Zinkin	1968	102	Depressive illness	BL (50) UL (52)	5-6 H	Self administered depression rating scale	NSS: between groups.	Instrument may not be standardized.
Costello	1970	30	Inpt primary problem "depression"	BL (10) ULD (10) ULND (10)	28-31 H	BDI Costello Comrey Depression Scale	NSS: between groups	ECT represented first course of ECT treatment the patient underwent.
Fleminger	1970	29	Depressed referred for ECT	BL ULD ULND	3 D 4 W	BDI	NSS: between groups SS: all groups change from baseline	
Rosenberg	1984	35	Major affective or schizoaffective disorder (DSMIII)	BL UL	1W	HRSD	NSS: between groups difference SS: all groups change from basleine.	
Gregory	1985	69	Depressive illness	BL UL sham	<2 D 1 M 3 M 6 M	HRSD MADRS, PIRS	SS: UL and BL significantly improved compared to sham NSS: UL and BL	
Horne	1984	48	MDD RDC	BL placebo (12) BL Dexameth (12) UL placebo (12) UL Dexameth (12)	<1 D	HRSD BPRS BDI	NSS: between groups SS: change from baseline	Combined across placebo and dexamethasone groups. Dexamethasone may impede recovery of depression
Ranjkesh	2005	45	MDD	BF 1.5ST BT ST RUL 5ST	1 D	HRSD24	NSS: all groups	BF moderate dose has same effectiveness as RUL or BL.
Pettinati	1984	28 15 13		BL (15) RUL (13)	1 W	HRSD BDI	B: pre 21.6 (7.9), post 11.5 (7.9) U: pre 21 (10), post 9.3 (7.2)	Right handed
Stoppe	2006	39	MDD, geriatric	RUL >5ST (17) BL 50% max (22)	1 D	MADRS	Remission: RUL 15 of 17 BL 15 of 22RUL: pre 32.76(7.99) to BL: pre 38.05(6.61)	Ungraph

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
CGIS: clinical global impression scale
CPRS: comprehensive psychiatric rating scale
CPZ: chlorpromazine
GP: global psychopathology
D: day
DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MASS: Montgomery Asberg Schizophrenia Scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
PIRS: psychological impairments rating scale
PSE: Present state examination
SANS: scale for the assessment of negative symptoms
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant
T3: tri-iodothyroxine
UBP : ultrabrief pulse
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 12. RCTs Included in Systematic Review of Effectiveness: Frequency of Treatment (Two Times vs. Three Times per Week) for Depression

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Gangadhar	1993	30	MDD, melancholicsubtype	2x per week (15) 3x per week (15)	24-48 H 6 M	HRSD CGI	NSS: no between groups difference SS: improvement from baseline	2x per week group received 1 sham per week ECT: BL treatment
Lerer	1995	52	MDD, endogenous	2x per week (23) 3x per week (24)	1 W 1 M	HRSD	NSS: no between groups difference SS: improvement from baseline	
Shapira	1998	31	Major Depression, endogenous subtype	2x per week (14) 3x per week (17)	1 D	HRSD	NSS: between groups continuous analysis SS: 2x per week more responders than 3x per week. 3x per week, faster response, but have same antidepressant outcome.	ECT: BL treatment, up to 8 sessions. 2x per week group received 1 sham per week
Janakiramaiah	1998	40	MDD with melancholia (DSM-IIIR)	1x per week high dose 1x per week low dose 3x per week High dose 3x per week Low dose	48 H 1M	HRSD	SS: at 48 H, improvement from baseline all groups SS: at 48 H, 3x per week more improvement than 1x per week	
McAllister	1987	20	MDE (DSM-III)	2x per week 3x per week	2 W, 4 W after initiation of trial	HRSD BDI	NSS: no between groups difference SS: improvement from baseline at 4 W	ECT UL treatment
Segman	1995	47	MDE, endogenous subtype (RDC)	2x per week (23) 3x per week (24)	1 W	HRSD	NSS: no between groups difference, trend favoring 3x per week.	Responder analysis

Abbreviations:
ATI: amitriptyline

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CGI: clinical global impression
CPRS: comprehensive psychiatric rating scale
CPZ: chlorpromazine
GP: global psychopathology
D: day
DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MASS: Montgomery Asberg Schizophrenia Scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
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PIRS: psychological impairments rating scale
PSE: Present state examination
SANS: scale for the assessment of negative symptoms
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant
T3: tri-iodothyroxine
UBP : ultrabrief pulse
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 13. RCTs Included in Systematic Review of Effectiveness: ECT vs. Sham for Schizophrenia

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measure	Outcome	Comment
Miller	1953	30	Schizophrenia, catatonic	1. Sine ECT x 3W (10) 2. Nonconvulsive ECT x 4W (10) 3. Pentothal x 4W (10)	3 W 4 W	Non standard functional measures	NSS all groups.	Non standard functional measures. Not included in systematic review.
Baker	1958	48	Schizophrenia	ECT (x 20) (18) Insulin coma (x 30) (15) Largactil (CPZ)10 mg tid (15)	Immediately post treatment	Wittenborn rating scale	NSS: Slight evidence in favor of ECT, med group significantly higher relapse	No sham comparison.
Brill	1959	97	Schizophrenia (67), schizoaffective or depression (30)	1. ECT 2. ECT succinylcholine 3. ECT thiopental 4. thiopental 5. nitrous oxide	1 M	Clinical assessment scale, Lorr scale	NSS: ECT vs. non-ECT groups	Single blind, Mixed diagnoses: schizophrenia primary. Subjects received up to 20 treatments. Schizoaffective group responded more than depression group.
Doongaji	1973	86	Schizophrenia	1. ECT ULD (18) 2. ECT ULND (17) 3.ECT BL (19)	1 D	BPRS	NSS: all groups	
Taylor	1980	20	Paranoid Schizophrenia	1. ECT (10) 2. Sham (10)	2, 4, 8, 16 W	CPRS, GP PSE, BDI	SS: ECT better than sham at 2, 4, 8 W, not at 16 W	
Bagadia	1983	22	Schizophrenia	1. Sham and CPZ 2. ECT and placebo	7 D 20 D	BPRS, CGI	SS: between groups 7 D NSS: 20 D SS: baseline change both groups	
Brandon	1985	19	Schizophrenia	CPZ and, 1. ECT (9) 2. Sham (8)	4 W 12 W 28 W after initiation of trial	MASS	Continuous SS: between groups at 4 W NSS: 12, 28 W	8ECT treatments. Also on CPZ.
Abraham	1987	22	Schizophrenia	Trifluoperazine and, 1. ECT x 8 (11) 2. Sham x 8 (11)	Every 2 W to 6 M	BPRS	SS: ECT better to 8 W, then NSS 12 W on.	No previous ECT for subjects. 8 total treatments. ECT leads to more rapid response.

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measure	Outcome	Comment
Sarkar	1994	30	Schizophreniform, 1st episode, brief duration	Haloperidol and, 1. ECT BL sine 2. Sham	1-6 W, 6 M	BPRS	NSS: at any time point, including 6 M	All subjects also received haloperidol 15 mg at bedtime. . Sine wave ECT.
Chanpattana	2000	62	Schizophrenia	Flupenthixol 12-24 mg) and, 1. BL ECT 1 ST (21) 2. BL ECT 2 ST (21) 3. BL ECT 4 ST (20)	1 W	BPRS (18 item x 0-6), GAF, MMSE	NSS: response rate all groups	Hi dose BL ECT speeds clinical response in pts with sz
Ukpong	2002	16	Schizophrenia	CPZ and, 1. ECT (9) 2. Sham (7)	2, 4, 6, 8, 12, 16, 20 W	BPRS, SANS, CGIS	NSS: ECT vs. sham	All subjects also received CPZ 300 mg daily

Abbreviations:
ATI: amitriptyline
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BL: bilateral
BT: bitemporal
CGIS: clinical global impression scale
CPRS: comprehensive psychiatric rating scale
CPZ: chlorpromazine
GP: global psychopathology
D: day
DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MASS: Montgomery Asberg Schizophrenia Scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
PSE: Present state examination
SANS: scale for the assessment of negative symptoms
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant

T3: tri-iodothyroxine
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 14. RCTs Included in Systematic Review of Effectiveness: ECT vs. Sham for Mania

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measure	Outcome	Comment
Sikdar	1994	30	Mania	1. ECT (15) 2. Sham (15)	Post 8th treatment	Mania rating scale	SS: ECT better than sham	Ss also received CPZ 600 mg daily thru tx 6
Mukherjee	1988	20	Mania	1. ECT BL 2. ECT RUL 3. ECT LUL 4. Lithium/haloperidol	Post treatment	"responder" MMS (modified mania scale)	UL ECT may be as effective as BL	Combined data from 2 studies; pilot 6subjects RUL or LUL2nd BL, full UL, Lithium/Haldol. Cross over phase if needed.
Barekatian	2008	28	Mania	1. ECT BF mod energy (14) 2. ECT BT low energy(14)	After 6 ECT and post-treatment	YMRS HRSD	NSS: After 6 and final, YMRS no difference, BF mod less MMSE decline	
Hiremani	2008	36	Mania	1. ECT BF (17) 2. ECT BT(19)	21 D	YMRS	SS: BF quicker decline than BT	
Mohan	2009	50	Mania	ECT BL ST (26) ECT BL 2.5ST (24)	Post treatment	YMRS, CGI, MMSE, WMS, autobio mem scale	Dichot: CGI data. Cont: YMRS unusable. Cognitive data usable. NSS: between groups	Twice per week ECT, both groups 90+% subjects significantly improved. 88% both groups remitted. Antipsychotics, BDZ allowed
Small	1986	33	Mania	1. ECT (17) 2. Lithium (16)	Post Treatment	CGI, BPRS, HRSD, Bech Rafaelson Manic Scale	NSS: no between groups difference, SS: improvement from baseline	Manic symptoms an indication for BL ECT.

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
CGIS: clinical global impression scale
CPRS: comprehensive psychiatric rating scale
CPZ: chlorpromazine
GP: global psychopathology
D: day
DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MASS: Montgomery Asberg Schizophrenia Scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
PSE: Present state examination
SANS: scale for the assessment of negative symptoms
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant
T3: tri-iodothyroxine
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale
YMRS: Young Mania Rating Scale

Table 15. RCTs Included in Systematic Review of Effectiveness: Electrode Placement by Energy Dose for Depression

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Fraser	1980	29	Depressive illness, geriatric	ULND BL	1 D 3 W	HRSD	NSS: UL = BL at either time point	
Weiner	1986	53	MDD, RDC	Pulse UL Sine UL Pulse BL Sine BL	6 M	HRSD Zung self rating depression scale	NSS: all groups SS: baseline change in ECT groups	21 controls who received no ECT
Janicak	1991	27	Depressed	ULND BL	3-5 D 6 M	HRSD24	NSS: between groups SS: improvement from baseline at both time points	
Sackeim	2000	80	MDD, RDC	RUL 1.5ST RUL 2.5ST RUL 6ST BL 2.5ST	1-2 D 1 W	HRSD CGI	SS: BL and RUL hi better than RUL moderate or low energy	RUL high energy is as effective as BL, less cognitive effects
Sackeim	2008	90	MDE, RDC DSMIV	RUL 6ST BP RUL 6ST UBP BL 2.5ST BP BL 2.5ST UBP	2 D 1 W	HRSD BDI, CGI	SS: UBP BL worse than other 3 groups.	Ungraph
McCall	2000	72	MDE DSM IIIR	RUL 2.25ST RUL fixed hi	1-2 D	HRSD21	SS: high dose RUL better than moderate dose NST: change from baseline	
Heikman	2002	24	MDE	RUL 5ST RUL 2.5 ST BF ST	1-3 D	HRSD 17	SS: high dose RUL faster response than low dose BF. NSS: trend toward higher response with high dose RUL	
McCall	2002	77	MDE	RUL 8ST (40) BL 1.5ST (37)	1-3 D 2 W 4 W	HRSD21 BDI	NSS: RUL 8ST not different then BL1.5 ST NST: but appears to	

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
							be some improvement from baseline, then relapse	
Eschweiler	2007	92	Pharmacoresistant major depression	BF RUL	1 D	HRSD21	NSS: between groups difference	
Kimball	2009	66	MDE, DSMIIIR	Moderate titrated RUL Fixed high dose RUL	1-2 D	HRSD21	NSS: between groups difference	
Kellner	2010	230	Bipolar and unipolar depression	BF 1.5ST BT 1.5 ST (72) RUL 6ST (77)	24-36 H	HRSD24	SS: All 3 groups had improvement from baseline. BT more rapid response	Remission categorical data as well
Taylor	1985	37	Melancholia (DSM-III)	BL (15) RUL (22)	48-73 H	HRSD15	Both demonstrate significant clinical improvement. SS: BL better	
Levy	1968	40	Depression	UL BL	6 H	Cronholm Ottosson	NSS trend for BL	35 J for all treatments
Zinkin	1968	102	Depressive illness	BL (50) UL (52)	5-6 H	Self administered depression rating scale	NSS: between groups.	Instrument may not be standardized.
Costello	1970	30	Inpt primary problem "depression"	BL (10) ULD (10) ULND (10)	28-31 H	BDI Costello Comrey Depression Scale	NSS: between groups	ECT represented first course of ECT treatment the patient underwent.
Fleminger	1970	29	Depressed referred for ECT	BL ULD ULND	3 D 4 W	BDI	NSS: between groups SS: all groups change from baseline	
Rosenberg	1984	35	Major affective or schizoaffective disorder (DSMIII)	BL UL	1W	HRSD	NSS: between groups difference SS: all groups change from basleine.	

First Author	Year	N	Subjects	Comparison	Time point	Efficacy Measures	Outcome	Comment
Gregory	1985	69	Depressive illness	BL UL sham	<2 D 1 M 3 M 6 M	HRSD MADRS, PIRS	SS: UL and BL significantly improved compared to sham NSS: UL and BL	
Horne	1984	48	MDD RDC	BL placebo (12) BL Dexameth (12) UL placebo (12) UL Dexameth (12)	<1 D	HRSD BPRS BDI	NSS: between groups SS: change from baseline	Combined across placebo and dexamethasone groups. Dexamethasone may impede recovery of depression
Ranjkesh	2005	45	MDD	BF 1.5ST BT ST RUL 5ST	1 D	HRSD24	NSS: all groups	BF moderate dose has same effectiveness as RUL or BL.
Pettinati	1984	28	28 15 13	BL (15) RUL (13)	1 W	HRSD BDI	B: pre 21.6 (7.9), post 11.5 (7.9) U: pre 21 (10), post 9.3 (7.2)	Right handed
Stoppe	2006	39	MDD, geriatric	RUL >5ST (17) BL 50% max (22)	1 D	MADRS	Remission: RUL 15 of 17 BL 15 of 22RUL: pre 32.76(7.99) to BL: pre 38.05(6.61)	Ungraph

Abbreviations:
ATI: amitriptyline
BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
CGIS: clinical global impression scale
CPRS: comprehensive psychiatric rating scale
CPZ: chlorpromazine
GP: global psychopathology
D: day

DRS: depression rating scale
HRSD: Hamilton Rating Scale for Depression
IMI: imipramine
M: month
MADRS: Montgomery Asberg Depression Rating scale
MASS: Montgomery Asberg Schizophrenia Scale
MDD: Major depressive disorder
MDE: Major depressive episode
MMPI: Minnesota Multiphasic Personality Inventory
NSS: Not statistically significant
NST: No statistical test reported.
PIRS: psychological impairments rating scale
PSE: Present state examination
SANS: scale for the assessment of negative symptoms
SS: statistically significant
STAI: state trait anxiety inventory
RDC: research diagnostic criteria
RUL: right unilateral
TCA: tricyclic antidepressant
T3: tri-iodothyroxine
UBP : ultrabrief pulse
VAS: visual analogue scale
W: week
WPRS: Wittenborn Psychiatric Rating Scale

Table 16. Risks/Adverse Events and Proposed Mitigation Factors

Risk/Adverse Event	Types	Risk Characterized	Proposed Mitigation Factors	Regulatory Mechanism
Alterations in blood pressure	Hypotension, hypertension	Hypertension a known very common risk of ECT.Risk may increase with co-morbid medical conditions. Hypotension a common risk of ECT, may be due to underlying cardiac disease or iatrogenic. Medical work up and management may mitigate risk.	• Pre-ECT assessment (including pertinent history taking, physical examination, EKG, echocardiogram, chest x-ray, pulmonary function tests, bronchoscopy, lab tests, and neuroimaging) •Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation) •Appropriate clinical management to minimize the risk of ECT	User labeling (physician and patient)
Cardiovascular complications	Arrhythmias, ischemia	Known common risk of ECT. Risk may increase with co-morbid cardiac condition. Medical work up and management may mitigate risk.	•Pre-ECT assessment (including pertinent history taking, physical examination, EKG, echocardiogram) •Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation) •Appropriate clinical management (e.g. use of anti-arrhythymic agents)	User labeling (physician and patient)
Cognition	Orientation/reorientation, executive function, global cognition	Generally occurs post-treatment, but typically resolves minutes after completion of treatment.	•Exclusive use of square wave, direct current, brief pulse waveform stimulus •Use of ultrabrief pulse (0.3 msec) stimulus •Exclusive use of unilateral nondominant electrode placement •Use of bifrontal electrode placement •Frequency of treatment no greater than twice weekly during a course of ECT	User labeling (physician and patient)
Dental/oral trauma	Dental fractures, lacerations, bleeding	Rare reports in public docket responses and MAUDE database.	•Pre-ECT dental assessment •Use of mouth protection (bite blocks)	
Device malfunction	Mechanical malfunction, software malfunction, inaccurate charge delivery, faulty electrode functioning.	Reports in MAUDE database and report from manufacturer docket.	• Adherence to electrical standards • Adherence to software • Development standards • Adherence to mechanical design standards • Bench testing (to characterize device output)	Standards, testing

Risk/Adverse Event	Types	Risk Characterized	Proposed Mitigation Factors	Regulatory Mechanism
			• Electrical safety testing • Biocompatibility testing (e.g. for electrodes)	
	Anterograde verbal, Anterograde nonverbal, Retrograde autobiographical, Retrograde impersonal,	Generally memory dysfunction occurs, but resolves over time. Autobiographical memory dysfunction is longer lasting, with limited data suggesting complete resolution at 6 months.	•Exclusive use of square wave, direct current, brief pulse waveform stimulus •Use of ultrabrief pulse (0.3 msec) stimulus •Exclusive use of unilateral nondominant electrode placement •Use of bifrontal electrode placement •Frequency of treatment no greater than twice weekly during a course of ECT	User labeling (physician and patient)
Pain/somatic discomfort	Headache, somatic pain, muscle soreness, dizziness	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited. May be treated with medication.	As needed use of clinically appropriate analgesic medications before, during or after the administration of ECT	User labeling (physician and patient)
Physical trauma	Fractures	Rare with the use of general anesthesia and neuromuscular blocking agents.	Use of general anesthetic agents and neuromuscular blocking agents	User labeling (physician and patient)
Prolonged seizures	Including status epilepticus	Rare reports in public, docket responses, MAUDE database and in the literature. May be exacerbated by medications and conditions that lower seizure threshold. Medical work up and management may mitigate risk.	Pre-ECT evaluation that assesses the risk of prolonged seizures (i.e. complete medical assessment and history, neurological history, medication history), clinically appropriate management of medications that alter the seizure threshold, and quick access to EEG	User labeling (physician and patient)
Pulmonary complications	Prolonged apnea, aspiration	Apnea related to slow metabolism of succinylcholine. May use alternative nondepolarizing muscle blocker. Aspiration an uncommon, but known risk of general anesthesia.	•Pre-ECT assessment (including pertinent history taking, physical examination, chest x-ray, pulmonary function tests, lab tests) •Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation) •Appropriate clinical management (mask ventilation, oxygen supplementation)	User labeling (physician and patient)
Skin burns	From poor electrode contact	Rare with proper skin preparation.	Proper skin preparation, including the use of conductivity gel,	User labeling (physician and patient)

Risk/Adverse Event	Types	Risk Characterized	Proposed Mitigation Factors	Regulatory Mechanism
Stroke	Hemorrhagic or ischemic	Rare reports in public, docket responses, MAUDE database and in the literature. Risk may increase with co-morbid intracranial pathology.Medical work up and management may mitigate risk.	•Pre-ECT assessment (including pertinent history taking, physical examination, and neuroimaging) •Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation •Appropriate clinical management (e.g. blood pressure control)	User labeling (physician and patient)
Auditory complications	Decreased acuity, hyperacuity, tinnitus	Rare reports in public docket responses and MAUDE database.	None proposed.	
Coma		Some reports in public docket responses and MAUDE database.	None proposed.	
Death/reduced life span		Literature review suggests mortality rate of 1:10,000 patient, or 1:80,000 treatments. This rate is on the order of minor surgical procedures.	None proposed.	
General functional disability	Problems attending to activities of daily living, work	Common complaint associated with ECT which may result in significant effects on the experience of the patient.	None proposed.	
General motor dysfunction	Weakness, tremor, gait disturbance, balance, residual muscle twitches	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited.	None proposed.	
Homicidality	Ideation and attempts	Rare reports in public docket responses and MAUDE database. No indication of increased risk in the literature.	None proposed.	
Iatrogenic	Adverse reaction to anesthetic agents/neuromuscular blocking agents	Rare reports in public docket responses, MAUDE database, and literature. Risks of general anesthetic agents and neuromuscular blockers known. Risk is low, but potentially severe.	None proposed.	
Nausea		Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited. May be treated with medication.	None proposed.	
Neurological symptoms	Paresthesias, dyskinesias	Fairly common report in public docket responses, and MAUDE database. Symptoms are generally not severe and time-limited.	None proposed.	

Risk/Adverse Event	Types	Risk Characterized	Proposed Mitigation Factors	Regulatory Mechanism
Neuropathological changes	gross anatomical structural changes, neurohistological changes	Literature review suggests no evidence of anatomical structural, histological, immunohistological or biomarkers of injury. Some studies suggest neuroproliferative effect	None proposed.	
Onset/exacerbation of psychiatric symptoms	Mood lability, manic switching, anxiety, panic/fear, subjective distress, personality changes, changes in motivation, apathy, catatonia, decreased responsiveness	Fairly common report in public docket responses, and MAUDE database. Causal attribution unclear.	None proposed.	
Sleep disturbance	Nightmares	Rare reports in public docket responses and MAUDE database.	None proposed.	
Suicidality	Ideation and attempts	Rare reports in public docket responses and MAUDE database. No indication of increased risk in the literature, and some suggestion that risk may decrease.	None proposed.	
Substance abuse	Use of illicit drugs	Rare reports in public docket responses and MAUDE database. No reports in the literature. Causal attribution unclear	None proposed.	
Urinary complaints	Hesitancy, incontinence	Some reports in public docket responses and MAUDE database. Symptoms are generally not severe and time-limited.	None proposed.	
Visual disturbance	Impairment, changes, corneal abrasion	Rare reports in public docket responses and MAUDE database.	None proposed.	

Appendix I. FDA Systematic Review: Memory and Cognitive Literature

Methods

This systematic review included only prospective, randomized controlled trials (RCTs) employing standardized cognitive tests and acceptable statistical comparisons to: (1) assess subjects' cognitive status before and after ECT and/or (2) compare outcomes between subjects randomized to ECT treatment conditions differing in electrode placement, dosage, or waveform or comparing ECT to sham ECT. From the initial search strategy described above, of the 1231 citations returned, and cross-referencing the existing systematic reviews and meta-analyses, 122 potential studies were considered for inclusion. Of those, 55 were excluded for various reasons (see Appendix). Sixty-seven (67) studies were examined in the systematic review of cognitive adverse events.

Cognitive domain classifications are not mutually exclusive as there is considerable overlap among various cognitive functions and robust correlations among specific domains. For example, tasks of attention and concentration often correlate with tasks of working memory and short-term memory as the constructs underlying these cognitive functions can be the same and, in some cases, may share common putative anatomical and physiological substrates (e.g., fronto-striatal pathways). By convention, the practice of clinical neuropsychology characterizes cognitive function into the following categories:

- Global cognitive function – often used in the screening of general mental status usually by a non-neuropsychologist at the bedside (e.g., Mini-Mental State Examination [MMSE])
- Orientation - awareness of self in relation to one's surrounding (e.g., identification of person, place, and time)
- Executive function – capacity to attend to, plan, organize and execute a behavioral response, including but not limited to:
    - Attention/concentration
    - Mental tracking, planning, organization and execution of motor/behavioral response
    - Problem-solving, judgement and reasoning
    - Response inhibition
    - Set-shifting
    - Working memory (capacity to hold information in short term storage in order to execute a cognitive response)
- Memory function – including capacity to recall previously learned (and stored) information, both personal and impersonal and the ability to encode, store and recall (recognize) novel information. Assessment of memory must include both verbal and non-verbal information. Review of the ECT literature on mnemonic function includes the following terminology:
    - Global Memory Function – typically a comprehensive battery of tests assessing attention/concentration, retrograde (impersonal) memory, and various verbal and non-verbal anterograde memory task (e.g., Wechsler Memory Scale [WMS])

    - Anterograde Memory – capacity to encode, store and retrieve novel information verbally and non-verbally after a course of ECT therapy (typically includes assessment of both free delayed recall and cued recognition)
    - Retrograde Memory – capacity to retrieve information encoded *prior* to initiation of ECT therapy:
        - Personal (autobiographical) memory – typically reported as a percent recall of baseline-established past personal information and events
        - Impersonal memory – capacity to recall historical or factual information (e.g., past presidents, direction of sunset, etc.)
    - Subjective Memory – typically a patient self-report inventory of perceived memory problems following a course of ECT treatment
- Language function – capacity to express and comprehend linguistic material and often includes assessment of fluency, naming, comprehension, reading, writing and arithmetic calculations
- Visuospatial function – capacity to understand and carry out activities dependent upon intact spatial abilities, including visuomotor, visuoconstructive, and perceptual (motor-free) tasks.
- Praxis/Gnosia – capacity to carry out previously learned activities (e.g., buttoning a shirt)/the perceptive faculty enabling one to recognize the form and the nature of persons and things
- Time to reorientation (specific to studies examining effects of ECT immediately during the "post-ictal" period) and typically includes ratings of confusion, orientation and delirium

The specific neuropsychological or cognitive tasks identified in the published studies in the FDA systematic review of the cognitive AE's following ECT included the following measures:

1. Confusion/Disorientation following ECT:
    - Time to reorientation (minutes) following ECT
    - Gresham Battery General Orientation subtest
    - Clinician confusion rating scale
2. Global Cognitive Function:
    - Mini Mental State Evaluation (MMSE) or modified MMSE
    - Halstead-Reitan Battery, Luria-Nebraska Battery, Aphasia Screening Test, tachistoscopic stimulation tests, and evaluation of soft neurologic signs
3. Global Memory Function:
    - Wechsler memory scale (WMS)
4. Executive Function:
    - Stroop Color-Word Interference (Stroop)
    - Continuous Performance Task (CPT)
    - Kornetsky-Mirsky Continuous Processing Task
    - Trail Making Test – Part A & B
    - Letter Number Sequencing Test (LNS)
    - Wisconsin Card Sorting Test (WCST)

- Delis-Kaplan Executive Function Sorting Test (D-KEFS)
- Alphabetic Cross-Out Test (ACOT)
- Pauli Test
- Mental control and Digit Span (from Wechsler Memory Scale)
- Thurstone Word Fluency Test (TWFT)
- Random Number Generation task
- Various cancellation tasks (e.g., letters, numbers, figures)
- Verbal fluency

5. Retrograde memory – Personal (Autobiographical) Memory
    - Columbia University Autobiographical Memory Interview (AMI); AMI-Short Form (AMI-SF);
    - Duke Personal Memory Questionnaire
    - Personal and Impersonal Memory Test, personal component (PIMT-P)
    - Wechsler Memory Scale Part I—Personal and Current Information
    - Recent Personal Events subscale of Gresham Battery (Gresham—RPE)
    - Autobiographical memory questionnaires
6. Retrograde memory - Impersonal Memory
    - Goldberg-Barnett Remote Memory Questionnaire (Goldberg-Barnett)
    - Personal and Impersonal Memory Test, impersonal component (PIMT-I)
    - General Events subtest of Gresham Battery (Gresham—GE)
    - Famous Faces Test
    - Wechsler Memory Test Information subscale (WMS-I)
    - Controlled Oral Word Association Test (COWAT)
7. Anterograde Memory – Verbal
    - Buschke Selective Reminding Test (SRT)
    - Paired word and short story recall portions of the Randt Memory Test
    - Rey Auditory-Verbal Learning Task (RAVLT)
    - Paragraph retention portion (WMS-P), Short Story (WMS-SS) or verbal portions (WMS-V) of Wechsler Memory Scale
    - Williams Verbal Learning Test (WVLT)
    - Modified Word-Learning Test (MWLT)
    - Paired Associates Learning Test (PALT); other verbal paired associates (VPA) or word recall tasks
    - Grunberger Verbal Memory Test—Associative Memory (GVM-A); Grunberger Verbal Memory Test—Common Memory (GVM-C)
    - Wechsler-Bellevue Intelligence Scale—Verbal IQ (WBVIQ)
8. Anterograde Memory – Nonverbal
    - Rey-Osterreith Complex Figure Test
    - Taylor Complex Figure Test
    - Medical College of Georgia Complex Figures (CFT)

- Face-label recall, face-label recall with cues, similar recall, recognition tasks
- Picture recall portion of the Randt Memory Test
- Visual reproduction portion of the Wechsler Memory Test (WMS-VR)
- Paired face tasks for recognition memory
- Graham-Kendall Memory for Designs Test (Graham-Kendall)
- Benton Visual Retention Test (Benton)
- Labyrinth subtest of the Nurnberg Age Inventory
- Wechsler-Bellevue Intelligence Scale—Performance IQ (WBPIQ)
- Bender-Gestalt Test
- Koh's Block Design Test
- Block Design (from Wechsler Adult Intelligence Scales)

9. Subjective memory
    - Squire Subjective Memory Questionnaire (SSMQ)
    - Patient subjective memory rating scale
    - Structured interview of subjective memory complaints

With regard to the assessment of retrograde personal (autobiographical) memory, the most commonly used measure was the Columbia University Autobiographical Memory Interview (AMI) questionnaire. The AMI (and the AMI short form, AMI-SF) was developed to standardize the collection of autobiographical data and to provide a range of time spans and item types (Kopelman et al, 1989). It contains two sections: an autobiographical incidents schedule and a personal semantic memory schedule. Each schedule contains questions from three time blocks: childhood, early adult life, and recent events. Initial validation of the AMI correlated the questionnaire scores with other remote memory tests, producing coefficients in the 0.27 - 0.76 range with most at or above .40 correlation. Amnestic patients performed significantly below control subjects on all variables, with the greatest difference between these groups occurring on the recent events memory score. Overall, this technique appears to satisfy practical requirements as a test of retrograde (remote) memory (Lezak, 1995). Thus, the AMI appears to have undergone some degree of psychometric standardization and has been the most commonly utilized task of retrograde personal memory assessment following ECT in the published literature. Therefore, we felt the AMI was a valid instrument for inclusion in our systematic review of retrograde (autobiographical) memory.

There are no published prospective RCTs without crossover between treatment groups that examined cognitive outcomes at more than 6 months after ECT. In addition, the type and severity of cognitive adverse events likely differ in relation to the time elapsed following a course of ECT. Therefore, for each of the above categories of cognitive function, available data on cognitive effects were categorized into five time points following ECT treatment:

- Immediately post-ECT: acute effects within 24 hours of ECT seizure termination
- Subacute effects: greater than 24 hours to less than 2 weeks after receiving a course of ECT
- Medium-term effects: 2 weeks to less than 3 months of receiving a course of ECT
- Longer-term effects: 3 months to less than 6 months of receiving a course ECT
- Long term effects: 6 months or greater after ECT

Results
The results of the FDA systematic review of published RCT's are presented by cognitive and memory domain.

1. Time to reorientation

Fourteen randomized controlled trials (n=966) assessed the length of time required for subjects to become reoriented immediately following administration of ECT. There are sufficient data to conclude that bilateral ECT is associated with longer disorientation than right unilateral, left unilateral, or unilateral non-dominant electrode placement. Similarly, bifrontal ECT is associated with longer periods of disorientation than bitemporal ECT, and high dose ECT is associated with longer disorientation than low or moderate dose ECT. There is no evidence that disorientation following ECT is long term or persistent.

2. Executive function

Six studies (n=251) assessed executive function immediately following ECT (up to 24 hours). Immediately following ECT, most data suggest that there is no significant change from baseline in executive function. There is no conclusive evidence that bilateral ECT is associated with greater executive dysfunction than unilateral ECT. No differences were found between bifrontal and bitemporal ECT. Brief pulse ECT showed greater acute executive dysfunction than ultrabrief pulse in one study. The literature suggests that there is no statistically significant decline in executive function from baseline in patients receiving a course of ECT therapy and that executive function may actually improve (possibly due to treatment of the underlying disorder).

In the sub-acute phase (24 hours to <2 weeks), there are 13 studies of executive function (n=958). There is conclusive evidence that executive function following bilateral ECT is not worse than unilateral ECT, and there is no significant change from baseline in this time period. Sine wave was not significantly different from pulse wave, and high energy was not significantly different from low energy. One study suggests that left unilateral ECT may be associated with greater executive dysfunction than right unilateral.

In the medium term (2 weeks to <3 months), there are 6 randomized controlled trials assessing executive function (n=251). With regard to executive function, there is conclusive evidence that there is no significant change from baseline. There is limited evidence that there is no difference between bilateral and unilateral ECT. There is limited evidence (1 study) that there is no significant difference between ECT and sham, pulse and sine waveforms, or between high and low energy.

There is limited long-term data on executive function. One study at 3 months (n=52) found that executive function following bilateral ECT was worse than unilateral and one study at 6 months (n=26) found no significant change from baseline on most measures and improvement on the Trail Making Test-A.

3. Global Cognitive Function

Immediately post-ECT (up to 24 hours), there are 4 studies (n=186) which assessed global cognitive function utilizing the Mini Mental State Examination (MMSE). Bilateral ECT shows significantly worse global cognitive performance than unilateral ECT in the acute phase in one study (the other studies did not yield statistically significant results). Therefore, there is no clear consensus as to change in global cognitive function from baseline.

Sub-acutely (24 hours to <2 weeks), there are 22 studies (n=1619) assessing global cognitive function. There is limited evidence that bitemporal ECT is worse than bifrontal ECT. There are 6 studies that find that bilateral ECT is worse than right unilateral ECT, but 7 that find no difference. One study finds that fixed high dose right unilateral ECT is worse than moderate titrated dose, but most studies do not show significant differences across different energy dosages. There is conflicting evidence regarding change from baseline in global cognitive function: 3 studies show decline, 8 studies show no change, and 4 studies show improvement.

In the medium term (2 weeks to <3 months), there are 3 studies (N=164). There were no differences in MMSE between ultrabrief pulse bifrontal compared to ultrabrief pulse unilateral ECT; both groups improved from baseline at 6 weeks. In manic patients there was no change from baseline at 2 weeks in MMSE.

From 3 months to <6 months, there is evidence from 2 studies (n=227) that there is no decline from baseline, and may be improvement or no change in global cognitive function from baseline. There are no stjudies examining the long term (>6 months) effects of Ect on global cognitive function.

4. Global Memory

One study (Martensson, 1994; n=25) demonstrates no significant difference in one measure of global memory (WMS logical prose) between baseline and immediately after the course of ECT treatment.

In the sub-acute period (24 hours to <2 weeks), there are nine studies (n=738). There were no significant differences between bilateral and unilateral ECT or between high and low dose ECT. There is equivocal data regarding change from baseline, with three studies showing a decline in global memory (including one 1968 study using sine wave ECT), and two studies showing no change from baseline.

In the medium term (2 weeks to <3 months), there are four studies (n=185) of global memory. The two studies that analyzed change from baseline demonstrated either no change or improvement. There are no data on differences in electrode placement at this time point. There was no difference between sine waveform and brief pulse ECT in one study and no difference by ECT dosing in another study. In one study, bilateral ECT three times per week resulted in significantly worse global memory decline than bilateral ECT twice per week.

There are no longer term studies (3 months to <6 months).

At 6 months, there are two studies (n=96). One study demonstrates no significant difference in global memory between real and sham ECT, and two studies show no significant change from baseline at 6 months.

5. Anterograde Verbal Memory

Studies comparing the effect of ECT versus sham on anterograde verbal memory are equivocal. However, immediately following ECT, there are sufficient data to demonstrate a decline in functioning from baseline. The results are equivocal with respect to electrode placement (bilateral vs. unilateral and bifrontal vs. bitemporal). Brief pulse may be associated with more memory dysfunction than ultrabrief pulse.

Sub-acutely (24 h to <2 weeks), there is sufficient evidence that left unilateral electrode placement is worse than right unilateral (four studies for, and one against); there is equivocal evidence that bilateral ECT is worse than unilateral, and sine is worse than pulse. There is also equivocal data with respect to baseline change scores. The studies reviewed demonstrate decline, no change and improvement thereby suggesting that no general conclusion can be drawn. These equivocal results may be accounted for, in part, by methodological considerations and include the possibility that different aspects of anterograde verbal memory may be differentially affected. Also, within this time frame, deficits may occur earlier and then resolve.

In the medium term (2 weeks to <3 months), there is sufficient evidence to conclude that there is no significant difference between bilateral and unilateral electrode placement. In terms of change from baseline, there are sufficient data to suggest that there is no change or improvement in anterograde verbal memory.

There are no longer term studies (3 months to <6 months).

At 6 months, no differences are observed between real ECT and sham, bilateral and unilateral and sine vs. pulse. An improvement from baseline is seen with continuation ECT and a typical course of ECT (two studies).

In summary, the findings regarding verbal anterograde memory impairment suggest the following:

a. Equivocal findings regarding verbal anterograde memory impairment in studies comparing the effect of ECT vs. sham
b. Bilateral electrode placement and left unilateral electrode placement appear to be associated with greater anterograde verbal memory impairment
c. Literature suggests that sine wave is associated with greater anterograde verbal memory impairment than brief pulse ECT
d. About 1 week after of ECT therapy, verbal memory function following right unilateral electrode placement and low/moderate energy dose ECT may return to baseline and might improve

e. About 2 after weeks of ECT therapy, verbal memory function following bilateral electrode placement may return to baseline and studies suggest that verbal memory might improve
f. There are limited data at 6 months post-ECT; there are some data to suggest that no differences are present between ECT and sham or bilateral vs .unilateral nondominant hemisphere electrode placement

6. Anterograde Non-verbal Memory

Immediately post-ECT, there are data that ECT (including maintenance ECT) may cause worse decline than sham or no ECT. There is likely no difference between bilateral and unilateral. No other significant differences were noted. Brief pulse may be worse than ultrabrief pulse. Studies show no change from baseline or a decline from baseline. Subacutely, sufficient data show that bilateral is probably no different than unilateral, and no other difference is seen between treatment parameters. There are equivocal findings regarding change from baseline with results indicating a wide range of change (decline, no change, improvement) with roughly a similar number of studies supporting these conclusions.

After 2 weeks, there is conclusive evidence that there is no difference between bilateral and unilateral, and insufficient evidence to support any differences between treatment parameters. There is conclusive evidence that there is either no change from baseline or improvement in this domain.

7. Retrograde Impersonal Memory. General conclusion: sufficient data

Immediately following ECT, there are four studies with data on retrograde impersonal memory (n=181). In one study, sham ECT resulted in poorer retrograde impersonal memory compared to real ECT, although retrograde memory improved over 8 hours following both real and sham ECT. In addition, there is some evidence that bilateral ECT was worse than unilateral, although both declined significantly from baseline although one study found no change from baseline.

Subacutely (24 hours to <2 weeks), there are eight studies (n=432) reporting retrograde impersonal data. Four studies show that bilateral ECT is worse than unilateral ECT, while another two studies did not detect a significant difference. Sine was worse than brief pulse ECT in one study, brief pulse was worse than ultrabrief pulse in one study, and there was no effect of ECT dose in one study. In four studies, there was a decline from baseline, particularly with bilateral ECT. There was no decline from baseline with ultrabrief pulse right unilateral ECT in one study and with unilateral non dominant ECT in another. In four additional studies there was no significant decline from baseline in retrograde impersonal memory.

For the medium term (2 weeks to <3 months) there are two studies of retrograde impersonal memory (n=90). Sham ECT was worse than real ECT at 1 month in one study. In another study, there was no significant difference between bilateral and unilateral non dominant ECT; the bilateral (but not unilateral) group improved significantly from baseline in retrograde impersonal memory.

There are no studies reporting retrograde impersonal memory data from 3 to <6 months following ECT.

There are four studies (n=189) with long-term data (6 months). No differences are seen between real and sham ECT (one study), bilateral and unilateral ECT (one study) and sine and pulse wave ECT (one study). There is no significant change from baseline in all three studies.

8. Retrograde Personal (Autobiographical) Memory

Immediately after ECT (<24 hours), there are five studies (n=249) of retrograde personal memory. Only one of four studies detected a difference between bilateral and unilateral ECT, with bilateral worse after six treatments. A decline from baseline in the acute period was reported in the two studies that examined change from baseline.

Subacutely (24 hours to <2 weeks), there are 14 studies (n=1456). Studies conclusively support the finding that bilateral ECT is associated with greater autobiographical memory impairment compared with unilateral, right unilateral or unilateral non-dominant ECT samples (ten studies); the one study that did not detect a difference compared high dose (8x seizure threshold) right unilateral to much lower dose (1.5x seizure threshold) bilateral ECT. Four studies show a decline from baseline, with the exception of an ultrabrief pulse group in one of these, which was unchanged. One additional study of ultrabrief pulse unilateral and bifrontal ECT showed improvement in retrograde personal memory compared to baseline at 1 and 6 weeks. One study demonstrated more impairment in sine ECT than brief pulse, and one demonstrated that brief pulse was worse than ultra brief pulse. Three studies detected no difference between low and high dose ECT at 1 week, while another demonstrated a worse outcome with fixed high dose vs. 2.25x seizure threshold right unilateral ECT at 1-2 days.

At the medium time frame (2 weeks to <3 months), there are six studies (n=319). There are limited data regarding the effects of electrode placement in this time period. Bilateral ECT was not significantly different than unilateral nondominant ECT in one study. There was no difference between ultrabrief pulse bilateral and ultrabrief pulse unilateral in another study, but unilateral dominant and bilateral were each significantly worse than unilateral nondominant ECT in a third study. There was no difference by dose in one study. While data are limited, there was improvement (when using ultrabrief pulse) or no change (one study) from baseline in retrograde personal memory.

From 3 months to <6 months, data are limited to two studies (n=159), with conflicting results regarding the effects of ECT on retrograde personal memory. One study (Weiner 1986; n=74) demonstrates that bilateral ECT is worse than unilateral non dominant and sine wave stimulus is worse than controls (not receiving ECT), with a trend for sine performing worse than brief pulse as well. This study shows a decline in retrograde personal memory over baseline at 6 months, though it appears that brief pulse unilateral treatment is similar to the recall shown by normal controls. Another study (Smith 2010; n=85) demonstrates that bilateral continuation ECT after an acute course of ECT is associated with worse autobiographical memory performance compared to continuation drug treatment at 12 weeks (compared to post-ECT course baseline scores). It is important to note that this difference is due to significant improvement over post-

ECT baseline in the continuation drug therapy group but no improvement or decline in the continuation ECT group at the 12 week time point, suggesting that this is not an effect of the presence (or absence) of depressive symptoms. This difference between continuation ECT and continuation drug therapy is no longer present at 24 weeks, and there is no significant change from post-ECT baseline at 24 weeks in either continuation drug therapy or continuation ECT in this study.

In terms of change from baseline, ten studies examining autobiographical memory using the AMI, PIMT-P (personal and impersonal memory test-personal portion; validated against the AMI), PMQ (personal memory questionnaire) or Duke personal memory questionnaire report % recall or (% amnesia) when comparing pre-ECT and post-ECT performance. These studies are listed in the Table 6. An examination of these non-randomized, within subjects, pre-ECT to post-ECT comparisons (within these studies employing and RCT methodology) demonstrates acute recall rates (within 1 week) of 70-90% with moderate to high dose RUL treatment, and 50-60% with high dose RUL treatment. BL treatment is associated with 40-70% recall within 1 week after ECT. Ultrabrief pulse stimulus (regardless of electrode placement) demonstrates 94% recall in the acute period. Finally, data from 2-6 months post treatment demonstrates recall rates 5-10% better than in the acute phase; at two months recall rates are 70% of baseline and at six months 80-90% of baseline (for non-sine wave stimulus).

9. Subjective Memory.

There are several methodological issues with regard to the use of self-reported, subjective complaints of memory impairment. Most notably, subjective memory assessment relies heavily on the use of self-report scales and appear highly dependent upon the time these scales are completed. Furthermore, subjective reports of memory impairment may be associated with the degree to which depressive symptoms resolve (Abrams, 2000). In general, patients are more likely to report memory impairment immediately following ECT treatment.

There are no randomized trials with data on subjective measures within the first 24 hours of administration of ECT.

Subacutely, from 24 hours to 2 weeks, there are sufficient data to conclude that bilateral ECT is associated with more subjective memory complaints than unilateral ECT. In terms of change from baseline, there is strong evidence that subjective memory reports demonstrate improvement after a course of ECT.

There is only one study with data for the medium term (2 weeks to <3 months) which reports no difference between unilateral and bilateral ECT at one month.

There are limited data on subjective memory function at six months. Overall, there appears to be no difference in subjective memory assessment between ECT and sham, or any of the ECT treatment factors. There is some evidence showing improvement or no change in subjective memory compared to baseline.

Appendix II. FDA Meta-Analysis: Memory and Cognitive Literature

Methods

Meta-analyses were conducted to evaluate both acute and sub-acute/medium-term cognitive adverse effects of electroconvulsive therapy (ECT). Published data were insufficient to evaluate longer-term effects through formal meta-analyses.

The criteria used to select studies for analysis were:

- There had to be at least two groups to compare within the study.,
- The selected studies had to have the same or cross-validated measures
- The studies had to have sufficient published data for analysis (number of patients per group, consistent continuous outcome measure reported and standard deviation).

Studies identified for inclusion compared some form of right unilateral (RUL) and bilateral (BL) electrode placement at low (about seizure threshold), medium (about 2.5 times seizure threshold) or high (about 5 times seizure threshold) energy levels. Three measures included in identified RCT studies were included in the meta-analyses: time to reorientation (measured in seconds), retrograde autobiographical memory (AMI, autobiographical memory interview) and cognitive status as measured by the Mini Mental State Examination (MMSE) right after ECT as well as 2 months after ECT. Using these criteria, the number of analyzable studies for all comparison was between two and four.

Meta-analyses were performed using the Intercooled Stata 9.2 software package. For continuous measures the 'metan' command was used to compute observed differences in means, to combine study outcomes and to display the results graphically via forest plots. A random effects model using the DerSimonian & Laird method (1986) was specified for each meta-analytical procedure.

Meta-analyses were conducted for the following cognitive domains:

- Time to reorientation (minutes)
- Mini-mental status examination (MMSE; global cognition)
- Autobiographical Memory Interview (AMI; retrograde autobiographical memory)

Results

To evaluate the acute effects of ECT, time to reorientation (in minutes) was considered (Sackeim 2000a, Sackeim 1993, Sobin 1995, Sackeim 2000b). Findings were consistent across comparisons (see Figures 6-10). The location of electrodes significantly affected time to reorientation (bilateral more than unilateral) increasing it by 18 seconds (unilateral medium vs. bilateral low) to 29 seconds (unilateral low vs. bilateral high). Patients receiving bilateral ECT at high doses had on average a 29-second longer time to reorientation compared to those patients receiving unilateral ECT at low doses. However, the effect of energy level seemed less relevant than electrode placement. Patients receiving unilateral ECT at low energy compared to those receiving unilateral ECT at medium energy had on average a time to reorientation that was 7 seconds longer, and there was no statistically significant difference comparing bilateral low to bilateral high energy levels.

Mini Mental State Examination (MMSE) was examined as a measure of general global cognitive function. Evaluation of the MMSE right after ECT (percent change from baseline (Sackeim 2000a, Sobin 1995), demonstrated a similar pattern (see Figures 11-15). Comparison of electrode placement ranged from a 6 to a 10 percentage points difference, showing that MMSE scores were worse after the bilateral placement compared to the unilateral placement, and there was no statistically significant difference in unilateral electrode placement low energy compared to medium energy and in bilateral electrode placement comparing low energy to high energy.

At two months post-course (Sackeim 1993, Sackeim 2000b), the percentage of MMSE items consistent with baseline showed statistically as well as clinically significant effects of ECT (see Figures 16-18). The percentage of inconsistent items ranging from 5 to 12 points, the largest difference being for the comparison unilateral low vs. bilateral high (i.e., higher values for a group indicate better cognitive performance; hence, a positive value for a difference between two groups in the forest plot indicate a poorer performance in the second group). Patients receiving bilateral ECT electrode placement at high dose had on average a percentage change in MMSE that was 12 points higher compared to those receiving unilateral electrode placement at low dose.

Retrograde autobiographical memory loss was evaluated using the Columbia University Autobiographical Memory Interview (AMI), based on the percent of items inconsistent with baseline (Sobin 1995, Sackeim 2000-J ECT). Evaluation of the AMI (% inconsistent with baseline) gave similar results to the time to reorientation in the acute phase (see Figures 19-23). Of note, all meta-analyses were conducted using data from the same two studies. Location of electrodes significantly affected retrograde memory, varying from 12 to 19 percentage points higher for bilateral compared to unilateral placement. There was no significant difference for energy with unilateral placement and a small difference of 7% for low to high energy with bilateral placement.

In summary, the effect of electrode placement appears to play a more important role in the acute cognitive adverse effects of ECT as measured by time to reorientation, global cognitive function and retrograde autobiographical memory compared to the level of energy used during the treatment.

Appendix III. FDA Systematic Review: Effectiveness Literature

Methods

The FDA team conducted its own systematic review of the existing literature.
The systematic review for effectiveness and safety of electroconvulsive therapy was conducted by searching PubMed, CINAHL and PsycINFO for all studies published through September 7, 2010. Search terms were included as both text and MESH headings and included the following: "major depression" "electroconvulsive therapy", "bipolar depression", "schizophrenia", "schizoaffective psychosis", "schizoaffective disorder", "catatonia", "mania", and "mixed states." Studies were limited to English, human, clinical trial, Cochrane review, controlled clinical trials, meta analyses, randomized controlled clinical trials, systematic reviews, research study, cohort study, case-control study, cross-sectional study, case study, observational study and case reports. Using this search strategy, 1231 citations were identified (See Table 2). These citations were cross-referenced with references provided from the manufacturer and public dockets and from bibliographies of published systematic reviews and meta-analyses; any additional titles were added for consideration.

Potentially suitable articles were requested via the FDA Biosciences Library. Practice guidelines were included if they were current and published by a professional or governmental organization charged with the oversight of a relevant aspect of psychiatric practice. Published systematic reviews and meta-analyses were included if they provided a comprehensive description of the search strategy and analysis.

Articles reporting primary data were included if ECT treatment was specified in the experimental protocol and the trial was a randomized, controlled design. This group of studies was evaluated for scientific rigor and relevance by review team members using a ranking system that evaluated the study design, quality of study, clinical relevance, study size, measures used and statistical analyses conducted.

The effectiveness review included only RCT's employing standardized assessments of psychiatric symptomatology. Effectiveness studies generally examined depressive, manic or psychotic symptom outcomes. Many studies did not make a distinction between unipolar major depressive disorder MDD and bipolar depression. Since several studies noted comparable effectiveness of ECT for unipolar and bipolar depression (Bailine et al. 2010; Medda et al. 2009), a decision was made to review depressive illness (both unipolar and bipolar) together. Several RCT's were identified for mania and schizophrenia; no RCT's were found for catatonia (See Appendix 1: Effectiveness Studies). Studies that examined a mixed diagnostic population were included in analyses where subject populations were $\geq 50\%$ of the total sample. Studies that examined subgroups of diagnostic populations (e.g., geriatric depression) were included in the analysis of the general diagnostic category. Meta-analyses were conducted for depressive illness and schizophrenia and studies were included if they used the Hamilton Depression Rating Scale (HRSD) or Brief Psychiatric Rating Scale (BPRS), respectively.

Following the methodology described above, RCT's were found for the following effectiveness study designs:

- Depression: ECT vs. Sham: 11 RCT studies
- ECT vs. Placebo: 6 RCT studies
- ECT vs. Antidepressants: 18 RCT studies
- Schizophrenia (ECT vs. Sham): 10 RCT studies
- Mania (ECT vs. Sham): 6 RCT studies
- Electrode placement (BL vs. UL) and Energy dose (low: ST-1.5 ST, moderate: 1.5ST-3ST, high: >3ST): 22 RCT studies

Results

1. ECT vs. Sham for Depression (See Table 9)

Eleven studies were identified as RCTs that examined depressive illness with appropriate sham comparator groups. All 11 studies reported results immediately post-ECT course. Three studies reported results one month or greater post-course.

In terms of immediate post-course effects, three studies conclude that ECT is more effective than sham (n=350) while three studies demonstrated no significant difference (n=64). Of the three studies that compared groups at one month or greater after the conclusion of the course, none demonstrated a significant difference between ECT and sham (n=171).

2. ECT vs. Placebo for Depression (See Table 10)

Six studies were identified as RCTs that examined depressive illness with a placebo comparator group. Time points ranged from immediately post-course to 6 months post trial initiation. All six studies (n=693) concluded that ECT is significantly more effective than placebo for shorter-term period. One study (n=126; ECT and placebo subjects) found that ECT was significantly better than placebo at 6 months (though, after 1 month of treatment, subjects could receive alternative treatments). Of note, given the nature of this comparison, subject blinding was a significant issue for this group of studies.

3. ECT vs. Antidepressants for Depression (See Table 11)

As a result of the literature search, the review team identified 18 RCTs involving a comparison between ECT and antidepressants (including imipramine, amitriptyline, phenelzine, tranylcypromine, paroxetine, lithium, and T3 for the treatment of depression. Given the nature of the comparison, ECT vs. medication treatment, only 4 studies utilized a double dummy design and were double blind to the ECT and medication groups. Also given the use of medication as a comparator group, this group of studies often defined time points relative to initiation of treatment.

For studies with a 4 week or shorter time point, five studies (n=310) demonstrated that ECT was significantly better than antidepressant medication while 7 studies (n=196) demonstrated that

there was not difference between ECT and antidepressant. One study (n=42) showed that imipramine was superior to ECT.

For studies with a greater than 4 week time point, two studies (n=409) demonstrated that ECT was significantly better than antidepressant while two studies (n=40) noted no significant difference.

Three studies (n=90) reported a statistically significant change from pre-ECT baseline to post-ECT follow-up.

4. ECT v Sham for Schizophrenia (See Table 12)

The review team identified ten RCTs examining the use of ECT for schizophrenia and employing an ECT vs. sham design. Five of the studies used adjunctive antipsychotic medications during the trial while three did not. Of the three strict ECT vs. sham studies, two (n=97) demonstrated no difference between ECT and sham, while one (n=20) demonstrated that ECT was better than sham at 2, 4 and 8 weeks, but not at 16 weeks. In the five studies that employed antipsychotic augmentation (one compared ECT to chlorpromazine administration), two studies (n=46) demonstrated no significant difference at any time point to 6 months, and three studies (n=63) had a similar pattern of an initial significant benefit of ECT becoming non-significant at later time points (7 days, 12 weeks). These findings offer preliminary support for a conclusion that ECT may not necessarily be more effective then pharmacotherapy, but may increase the speed of response.

5. ECT v Sham Studies for Mania (See Table 13)

The review team identified six RCTs examining the treatment of mania with ECT. Only one study utilized a real ECT vs. sham ECT design. This study of 15 subjects demonstrated that ECT was significant better than sham immediately post treatment. The other five studies examined different ECT placements or energy doses, and yielded variable results.

6. Effect of Electrode placement and Energy dose (See Table 14)

As a result of the literature search, the review team identified 22 RCTs involving a comparison between ECT bilateral and ECT unilateral electrode placement and/or modulation in energy dose. With regard to unilateral electrode placement, right unilateral (RUL) and unilateral nondominant (ULND) were combined, and left unilateral (LUL) and unilateral dominant (ULD) were combined. Bitemporal (BT; or bilateral (BL) placement, if not further detailed) were combined, while bifrontal (BF) placements were treated separately. With regard to dosing, in seizure threshold titration protocols, stimuli just above seizure threshold (ST) to 1.5 times seizure threshold (1.5ST) were considered low energy, 1.5 to 4 ST were considered moderate energy and > 4 ST was considered high energy.

In the acute setting (less than 2 weeks), 15 studies (n=900) demonstrated no difference between BL (BT) and RUL (ULND) placement, while five studies (n=290) demonstrated a significant

difference. One study (n=90) that examined UBP stimulus demonstrated a significant difference between UL and BL, with UL being associated with greater effectiveness. Three studies that examined BF vs. RUL treatment (n= 197; one using UBP stimulus) demonstrated no significant difference between electrode placements. In a longer term setting (greater than 2 weeks), two studies (n=80) demonstrated no difference between BL and UL placement at 3 weeks and 3 months post-ECT course.

In terms of energy dosage, three studies (n=128) demonstrated increased effectiveness of high energy dosing (especially with RUL electrode placement) versus moderate or low dose, while one study demonstrated no significant difference (n=67).

Nine studies (n=574) found a significant improvement between baseline and follow-up for individuals receiving any type of ECT treatment, with one study (n=27) demonstrating an effect as far out as six months.

7. Frequency of treatment: twice vs. thrice per week ECT (See Table 15)

Six studies were identified that compared the effectiveness of two times per week versus three times per week ECT during a course of treatment. These studies (n=133) demonstrated that at 1-4 weeks post-ECT course, both treatments demonstrated significant differences from baseline, but no significant differences were demonstrated between groups. One study at one month post-course and one study at six months post-course continued to demonstrate no significant difference between the twice per week and thrice per week group. There was also conclusive evidence that three times per week treatment was associated with more rapid improvement in depression symptoms, though three times per week treatment was also associated with more severe memory problems.

Appendix IV. FDA Meta-Analysis: Effectiveness Literature

From the initial pool of studies identified for the systematic review, studies were examined for their appropriateness of inclusion in the meta-analysis. Studies were determined to be meta-analyzable if they met criteria for inclusion in the systematic review, utilized comparable trial designs, examined comparable time endpoints and reported sufficient data to be utilized in a meta-analysis. A number of studies did not provide sufficient information about study design or provided insufficient data for meta-analysis; when possible, the authors were contacted directly to provide additional information. Of seven authors contacted, four provided additional information. Additionally, a number of studies provided necessary information in graphical format. In these cases, when possible, a software application, Ungraph, was utilized to transform the graphical representation to numerical data.

Effectiveness meta-analyses were conducted for Depression and Schizophrenia. Meta-analyses were not conducted for Mania or Catatonia, due to the lack of RCT data.

For depression, meta-analyses were conducted for the following comparisons:

- ECT vs. sham
- ECT vs. antidepressant drugs
- Bilateral (bitemporal) vs. Unilateral (ULND, RUL) (no dosage specified)
- Bilateral (bitemporal, low or medium dose) vs. Unilateral (ULND, RUL, high dose)

For schizophrenia, a meta-analysis was conducted for ECT vs. sham.

- Frequency of treatment: two times per week vs. 3x per week

1. Depression: ECT vs. Sham

As a result of the literature search, the review team identified 11 RCTs involving a comparison between ECT and sham for the treatment of depression. Each of these studies was evaluated for possible inclusion in a meta-analysis. The studies that reported means and standard deviations (SDs) of the change in the Hamilton Depression Rating Scale (HRSD) scores from baseline to an acute follow-up time in each treatment group were included in the meta-analysis.

The analysis of the data was based on a random effects model for the difference in mean changes (baseline to follow-up) between ECT and sham. In the analysis we assumed that the mean difference for each study was drawn from a normal population having a study-specific mean and variance. All study-specific means were assumed to come from a normal population with a mean representing the overall treatment effect of ECT relative to sham. This overall treatment effect was the parameter of interest in the meta-analysis.

After evaluating the 11 RCTs of ECT vs. sham, we found that the following studies could be included in the meta-analysis. Sample sizes and follow-up times are also specified.

- Wilson et al., 1963, n=6/group, 2 weeks
- Lambourn & Gill, 1978, n=16/group, 2 weeks
- Johnstone et al., 1980, n=31/group, 4 weeks
- Brandon et al., 1984, n=43 ECT, 29 sham, 4 weeks

- Jagadeesh et al., 1992, n=12/group, 2 weeks

The remaining studies were excluded, primarily due to lack of sufficient HRSD data:

- Palmer et al., 1981: subset of Brandon et al., 1984
- West, 1981, had BDI but not HRSD data
- Fink et al., 1958: no continuous data
- Harris & Robin, 1960: no continuous data reported
- Robin & Harris, 1960: no continuous data reported
- Fahy et al., 1963: no usable continuous data

Figure 24 summarizes the results of the meta-analysis obtained using a random effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the model. The overall estimate indicates that the mean improvement in HRSD for subjects treated with ECT was about 7.1 points (95% CI: -0.1, 14.2) greater than for those treated with sham therapy. A fixed effects model was also considered, and the effect of ECT was estimated to be 4.8 (95% CI: 1.2, 8.4).

2. Depression: ECT vs. Placebo

Three RCTs of ECT vs. placebo were identified (listed below), however none of these studies had sufficient HRSD to be included in a meta-analysis.

- Wilson et al., 1963, n=6/group
- MRC, 1965, n=58 ECT, 51 placebo
- Greenblatt et al., 1964, n=63 ECT, 39 placebo

3. Depression: ECT vs. Antidepressants

As a result of the literature search, the review team identified 18 RCTs involving a comparison between ECT and antidepressants (including imipramine, phenelzine, lithium, paroxetine) for the treatment of depression. Each of these studies was evaluated for possible inclusion in a meta-analysis. The studies that reported means and standard deviations (SDs) of the change in the Hamilton Depression Rating Scale (HRSD) scores from baseline to an acute follow-up time in each treatment group were included in the meta-analysis.

The analysis of the data was based on a random effects model for the difference in mean changes (baseline to follow-up) between the ECT and antidepressant groups. In the analysis we assumed that the mean difference for each study was drawn from a normal population having a study-specific mean and variance. All study-specific means were assumed to come from a normal population with a mean representing the overall treatment effect of ECT relative to sham. This overall treatment effect was the parameter of interest in the meta-analysis.

After evaluating the 18 RCTs of ECT vs. antidepressant, we found that the following 8 studies could be included in the meta-analysis. Sample sizes and follow-up times are also specified.

- Wilson, 1963, n=6/group, 5 weeks

- Davidson, 1978, n=9 ECT, 8 AD, 5 weeks,
- Panneer Selvan, 1999, n=14/group, 4 weeks
- Janakiramaiah, 2000, n=15/group, 4 weeks
- Steiner, 1978, n=4/group, 5 weeks
- Gangadhar, 1982, n=11 ECT, 13 AD, 4 weeks
- Dinan, 1989, n=15/group, 3 weeks
- Folkerts, 1997, n=18 ECT, 21 AD, 3 weeks

The remaining 10 studies were excluded due to lack of sufficient analyzable data:

- Bruce, 1960
- Harris, 1960
- Robin, 1962
- Fahy, 1963
- Greenblatt, 1964
- MRC study, 1965

Figure 25 summarizes the results of the meta-analysis based on a random-effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the model. The overall estimate indicates that the mean improvement in HRSD for subjects treated with ECT was about 5.0 points (95% CI: 0.8, 9.1) greater than for those treated with some form of antidepressant therapy. A fixed-effects model was also considered, and the effect of ECT was estimated to be 5.1 (95% CI: 2.7, 7.6).

4. Depression: Electrode Placement. Bilateral (Bitemporal) vs. Unilateral (Right or Nondominant)

As a result of the literature search, the review team identified 22 RCTs involving a comparison between ECT bilateral and ECT unilateral electrode placement. Each of these studies was evaluated for possible inclusion in a meta-analysis. The studies that reported means and standard deviations (SDs) of the change in the Hamilton Depression Rating Scale (HRSD) scores from baseline to an acute follow-up time in each treatment group were included in the meta-analysis.

The analysis of the data was based on a random effects model for the difference in mean changes (baseline to follow-up) between ECT bilateral and unilateral electrode placement. In the analysis we assumed that the mean difference for each study was drawn from a normal population having a study-specific mean and variance. All study-specific means were assumed to come from a normal population with a mean representing the overall treatment effect of ECT relative to sham. This overall treatment effect was the parameter of interest in the meta-analysis.

After evaluating the 22 RCTs of bilateral vs. unilateral ECT referred to above, we found that the following 5 studies could be included in this meta-analysis evaluating bilateral ECT against unilateral ECT without specification of dosage. Sample sizes and follow-up times are also specified.

- Fraser 1980, n=15 BL, 12 UL; 3 weeks
- Pettinati 1984, n=15 BL, n=13 UL; 3 weeks

- Rosenberg 1984, n=21 BL, 14 UL; 3 weeks
- Horne 1985, n=12/group; 3 weeks
- Taylor 1985, n=15 BL, 22 UL; 2 weeks

The results for this meta analysis are summarized in section 4.1 below.

The following 4 studies were found to have sufficient data to be included in a meta analysis of bilateral ECT (low or medium dose) vs. unilateral ECT (high dose).

- McCall 2002, n=37 BL, 40 UL; 4 weeks
- Ranjkesh 2005, n=14 BL, 12 UL; 3 weeks
- Sackeim 2008, n=23 BL, 22 UL; 1 week
- Kellner 2010, n=81 BL, 77 UL; 3 weeks

The results for this meta analysis are summarized in section 4.2 below.

The remaining 20 studies were excluded primarily due to lack of analyzable data (e.g., no standard deviation, insufficient data to calculate pre-post change).

4.1 Bilateral ECT vs. Unilateral ECT (no dosage specified)

Figure 27 summarizes the results of the meta-analysis based on a random-effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the meta-analysis model. The overall estimate indicates that the mean improvement in HRSD for subjects treated with bilateral ECT was about 4.0 points (95% CI: -0.6, 8.6) greater than for those treated with unilateral ECT. A fixed-effects model was also considered, and the effect of bilateral vs unilateral ECT was estimated to be 4.9 (95% CI: 1.7, 8.0).

4.2 Bilateral ECT (low or medium dose) vs. Unilateral ECT (high dose)

Figure 28 summarizes the results of the meta-analysis based on a random-effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the meta-analysis model. The overall estimate indicates that the mean improvement in HRSD for subjects treated with bilateral ECT was about 0.2 points (95% CI: -2.2, 2.6) greater than for those treated with unilateral ECT. A fixed-effects model was also considered, and the effect of bilateral vs unilateral ECT was estimated to be 0.2 (95% CI: -2.2, 2.6).

5. Schizophrenia: ECT v Sham

As a result of the literature search, the review team identified 6 RCTs involving a comparison between ECT and sham for the treatment of schizophrenia. Each of these studies was evaluated for possible inclusion in a meta-analysis. The studies that reported means and standard

deviations (SDs) of the change in the Brief Psychiatric Rating Scale (BPRS) scores from baseline to an acute follow-up time in each treatment group were included in the meta-analysis.

The analysis of the data was based on a random effects model for the difference in mean changes (baseline to follow-up) between ECT and sham. In the analysis we assumed that the mean difference for each study was drawn from a normal population having a study-specific mean and variance. All study-specific means were assumed to come from a normal population with a mean representing the overall treatment effect of ECT relative to sham. This overall treatment effect was the parameter of interest in the meta-analysis.

After evaluating the 6 RCTs of ECT vs. sham, we found that the following three studies could be included in the meta-analysis. Sample sizes and follow-up times are also specified.

- Abraham 1987, n=11,11; 4 weeks
- Sarkar 1994, n=15,15; 2 weeks
- Ukpong 2002, n=9,7; 3 weeks

The three remaining studies were excluded due to lack of sufficient analyzable BPRS data:

- Bagadia 1981
- Bagadia 1983
- Brandon 1985

Figure 26 below summarizes the results of the meta-analysis based on a random-effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the meta-analysis model. The overall estimate indicates that the mean improvement in BPRS for subjects treated with ECT was about 2.3 points (95% CI: -3.7, 8.3) greater than for those treated with sham therapy. A fixed-effects model was also considered, and the effect of ECT was estimated to be 2.2 (95% CI: -2.0, 6.3).

6. Depression: Frequency of Treatment. Two Times vs. Three Times per Week

Three studies were found that reported means and standard deviations (SDs) of the change in the Hamilton Depression Rating Scale (HDRS) scores from baseline to an acute follow-up time for subjects receiving either bilateral ECT two times per week (2x) or three times per week (3x). The three studies included in this meta-analysis are

- Gangadhar et al. (1993), n=15 (2x), n=15 (3x)
- Lerer et al. (1995), n=23 (2x), n=24 (3x)
- Shapira et al. (1998), n=14 (2x), n=17 (3x)

The analysis of the data was based on a random effects model for the difference (3x - 2x) in mean changes (baseline to follow-up) between the ECT 3x and ECT 2x groups. In the analysis we assumed that the mean difference for each study was drawn from a normal population having a study-specific mean and variance. All study-specific means were assumed to come from a normal population with a mean representing the overall treatment effect of ECT 3x relative to ECT 2x. This overall treatment effect was the parameter of interest in the meta-analysis.

Figure 29 summarizes the results of the meta-analysis obtained using a random effects model. The bottom-most segment in the plot shows the estimate (and 95% confidence interval) of the overall treatment effect. The other segments in the plot show the study-specific estimates of treatment effect (and 95% CI) as estimated from the model. The overall estimate indicates that the mean improvement in HDRS for subjects treated with ECT three times per week was about 1.1 points (95% CI: -5.0, 7.2) greater than for those treated with ECT twice per week. A fixed effects model was also considered, and the effect was estimated to be 1.1 (95% CI: -2.9, 5.1).

EXHIBIT 2

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DATE February 28, 2012

TO James M. Engles, M.S., M.B.A.
Designated Federal Officer
United States Food and Drug Administration
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FROM Moira Dolan, M.D.

RE ECT MACHINE SAFETY PROBLEMS
FDA Executive Summary
Prepared for the January 27-28, 2011 meeting of the Neurological Devices Panel
Meeting to Discuss the Classification of Electroconvulsive Therapy Devices (ECT)

FDA's selection of the medical literature regarding safety of ECT failed to obtain the objectives as mandated by the GAO.

ECT machines are "pre-amendment devices" that currently remain Class III. Until proven otherwise, it is presumed that insufficient information exists to assure the safety or effectiveness of the device through general or special controls. The current task of the FDA as demanded by the GAO is to determine 1.) if manufacturers of ECT machines should be required to submit pre marketing approval (PMA) for the devices, and 2.) if ECT machines should be reclassified as Class II devices.

The FDA stated that it set out to establish their answers to the above two questions for each of six diagnoses, including Depression (unipolar and bipolar), Bipolar manic (and mixed) states, Schizophrenia, Schizoaffective disorder, Schizophreniform disorder and Catatonia. However the literature often did not distinguish the types of depression or the types of schizophrenia, and there were no qualifying studies on catatonia. Thus of the seven intended categories to study, FDA only reviewed articles on three.

The FDA obtained comments through manufacturers and public dockets, Manufacturer and User Facility professional and/or governmental practice guidelines, Device Experience database (MAUDE), in addition to their own literature review. In order to satisfy the requirement of "well controlled investigations experiments", FDA limited their literature interest to randomized controlled trials (RCT).

Studies were included if they examined the following comparator groups: ECT vs. sham ECT, ECT vs. placebo, ECT vs. active medication, ECT utilizing different waveforms (i.e., sine wave, brief pulse, ultrabrief pulse), ECT utilizing different electrode placement (i.e., bitemporal, bifrontal, unilateral dominant, unilateral non-dominant), ECT utilizing different energy dosages, ECT with different frequency of treatment administration, ECT + intervention to optimize safety/effectiveness vs. ECT without intervention, Post-ECT course maintenance ECT vs. continuation medication treatment.

The following 17 points will illustrate the failure of the selected literature to demonstrate ECT machine safety, and in fact will show that the ECT machine is not safe:

1. Four of the comparator groups only compare ECT to itself, the variations being in terms of wave forms, electrode placement, energy dose and frequency of administration. These studies are not designed to furnish information about the definite safety and absolute effectiveness of ECT, only the relative safety and effectiveness compared to ECT delivered in some other fashion.

2. Two of the comparator groups compare ECT with or without additional measures, but do not establish whether ECT is safe or effective, and thus do not serve to answer the safety and effectiveness questions as mandated by the GAO.

3. Only three of the nine types of comparator groups included by FDA are true comparisons of ECT versus no ECT. The remaining six types of studies have no role in determining the safety and effectiveness of ECT. These comparator groups strictly address mitigation of adverse events. These studies have no role in the determination as to the safety and effectiveness of ECT. Such reports should not be under consideration until after safety and effectiveness of ECT has been demonstrated, and then only to establish if it were possible to put mitigating factors into place.

4. Regarding safety, FDA stated that it only included studies that utilized established psychiatric rating scales. However, the lack of meaningful interpretation of such scales is admitted in this statement by FDA:

> "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects". (ECT 515(i) Executive Summary Draft p.17, #5)

5. FDA admitted the obvious insufficiency of studies regarding the following serious, debilitating or deadly adverse effects:

> b. Personality changes caused or worsened by the treatment. FDA concluded: "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects."
>
> c. Mania, hypomania and manic switching caused or worsened by the treatment. FDA concluded: "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects."

d. Depression caused or worsened by the treatment. FDA concluded: "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects."

e. Anxiety, fear and panic caused or worsened by the treatment. FDA concluded: "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects."

f. Alterations in motivation caused or worsened by the treatment. FDA concluded: "Because ECT is used to treat psychiatric conditions, it is often difficult to distinguish between primary symptomatology and treatment-caused (or exacerbated) effects."

g. Coma has been reported following ECT. FDA concluded: "No systematic studies have been conducted to examine the association of coma and ECT."

h. Homicidality has been reported following ECT. FDA concluded: "No case reports or studies have been published examining this association."

i. Increased use of illicit drugs has been reported with ECT treatment. FDA concluded: "Given the increased co-morbidity of psychiatric illness and substance abuse, it is difficult to determine the cause of increased substance use associated with ECT. No systematic studies have been conducted to examine this association."

6. FDA admitted the obvious insufficiency of studies regarding the following less severe adverse effects that can contribute to increased morbidity after ECT:

a. Nightmares and sleep disturbance have been reported with ECT treatment. FDA concluded: "...no systematic studies have been conducted to examine this association".

b. Vision changes and eye trauma have been reported with ECT. FDA concluded: "...no systematic studies have been conducted to examine this association".

c. Changes in hearing have been reported with ECT. FDA concluded: "No systematic studies have been conducted to examine this association."

d. Urinary symptoms may be associated with ECT. FDA concluded: "No systematic studies have been conducted to examine the association of urinary symptoms and ECT."

7. In addition, FDA admitted reports of neurological and motor problems associated with ECT, but failed to identify adequate studies addressing the frequency, extent, duration and severity or latent incidence of these adverse effects.

a. Neurological symptoms including paresthesias, speech difficulty, loss of coordination, and gait or balance disturbance have been reported with ECT. FDA failed to identify adequate studies addressing the frequency, extent, duration, severity and incidence of late neurological symptoms with ECT.

b. General motor dysfunction including muscle weakness or paralysis, prolonged tremor, and residual muscle twitching/spasms have been reported with ECT. FDA failed to identify adequate studies addressing the frequency, extent, duration, severity and incidence of late motor dysfunction with ECT.

8. FDA found the literature to be sufficient to conclude that ECT is definitely associated with the following serious morbidities, yet failed to cite adequately controlled studies of sufficient duration to assess the long term consequences and to identify latent effects.

a. General functional disability. FDA found ECT-associated general debility to be relatively common and with significant effects, including:

i. Difficulties attending to activities of daily living.

ii. Loss of normal functioning.

iii. Difficulties with work.

iv. General decrease in quality of life.

b. Prolonged seizures have rarely been reported with ECT. However FDA fails to mention the more common occurrence of persistent seizure disorder, and omits the fact that there are no controlled studies of sufficient duration to assess the long term incidence of ECT-associated chronic seizure disorder.

c. Pain/discomfort. FDA found ECT-associated pain to be relatively common. Although FDA states pain is "time-limited", this is contradicted by mention of the use of medication for "prolonged" pain. FDA fails to mention that there are no studies of sufficient duration to assess the long term incidence and impact of ECT-associated pain and discomfort, including:

i. headaches

ii. body pains

iii. muscle pains

iv. dizziness

9. FDA found the literature sufficient to conclude that pulmonary and cardiovascular complications of treatment are among the most frequent causes of significant morbidity and mortality associated with ECT. However FDA fails to identify any study of sufficient size and data integrity to assess the frequency of these serious and at times deadly complications, including:

a. prolonged apnea

b. aspiration

c. hypertension

d. hypotension

e. cardiac arrhythmias

f. cardiac ischemia

10. FDA admitted the occurrence of ECT-associated stroke, with increased risk in patients with intracranial lesions, cerebral aneurysm or recent unrelated stroke. However the primary study cited is Hsiao et al., (1987) which was simply a summary of various case reports. FDA fails to admit that there are no well designed studies of sufficient size and design to identify the incidence of acute stroke and sub acute ischemic vascular brain injury.

11. FDA states there is no increased suicidality associated with ECT treatment based on observational studies, but the specifically cited articles do not substantiate any such conclusion.

a. FDA says, "Results of these studies have reported no increased suicidality associated with ECT treatment (Royal College of Psychiatrists [RCP] 2004)." This refers to a report formally titled "The ECT Handbook", subtitled "The Third Report of the Royal College of Psychiatrists' Special Committee on ECT" authored by Royal College of Psychiatrists (2004) and edited by AIF Scott. There is nothing in this 243-page report addressing ECT-associated suicide. The chapter which covers adverse effects of treatment is only three pages long and makes no mention of treatment-associated suicidality.

b. Other observational studies cited by FDA include Kellner, et al (2005), which interviewed patients about suicidal contemplation during a three week course of ECT but did not include any post-treatment follow up to track actual suicide attempts or completed suicides.

c. FDA cited a study by O'Leary, et al (2001) which calculated suicide rates during different treatment eras. According to this report, suicides were 42% more likely in the ECT era than in the antidepressant era. Thus this actually demonstrates the opposite from what is concluded in the FDA summary.

Notwithstanding the contradictions between the actual studies and the faulty FDA conclusion about ECT associated suicidality, comment must be made about FDA reliance on observational studies on this topic. It is remarkable that the observational studies regarding suicide were cited as substantial evidence, while the observational studies demonstrating increased mortality were discounted.

12. Despite the limitations of the selected reports, there was no disagreement on the fact that ECT causes memory loss. FDA concluded, "There is clear evidence that memory and cognitive impairment (i.e., orientation, retrograde memory, anterograde memory and global cognitive

function) occur both immediately after administration of ECT and following a course of therapy."

a. The evidence is insufficient to address the frequency, extent and duration of treatment-caused memory loss. FDA admits there are considerable problems in the medical literature regarding an accurate and reproducible assessment of memory loss. "Methodological issues such as lack of consistent definitions and use of nonstandardized cognitive instruments hamper assessment of cognition."

b. The medical literature selected by FDA on ECT –induced memory loss consists of 7 reviews or meta-analyses conducted within a 6-year period, plus one more recent meta-analysis. Each one of these overlap considerably in the actual original studies they included. The use of 7 overlapping reviews (and one 2010 update) deceptively over-represents the adequacy of the original literature.

c. FDA cites the Semkovska and McLoughlin (2010) meta-analysis of memory loss after ECT and admits that the studies analyzed did not examine retrograde autobiographical memory. This is despite FDA's acknowledgement that, "The primary type of retrograde memory affected is autobiographical memory." Retrograde autobiographical memory includes such essentials as knowledge of one's own identity, childhood and family memories, learning experiences, and work and travel history. It is not appropriate to include a study that omits addressing the single most commonly affected and most debilitating aspect of memory loss.

d. FDA indicates that the cited reviews and meta-analysis reports varied considerably in other aspects of memory loss, reflecting the lack of adequate studies in this field. For example:

i. FDA cites Rose, et al (2003) for estimating that memory loss ranges from 29% to 79%. Even this considerable variation ignores other reports (not included in the reviews) that show even greater variation ranging from 0 to 99%.

ii. FDA admits the evidence for determining the duration of memory loss is very limited. This crucial point which affects long term function has not been adequately studied.

iii. FDA admits that subjective reports of persistent memory loss are not adequately detected by some testing methods.

13. Cognitive losses after ECT are inadequately studied. FDA concludes: "There are no published prospective RCTs without crossover between treatment groups that examined cognitive outcomes at more than six months after ECT."

a. FDA admits to "...lack of RCTs utilizing the appropriate standardized scale, the appropriate comparison groups within a comparable timeframe, and sufficient reporting of results."

b. Due to the lack of adequate studies, FDA proceeded to draw conclusions from very small meta-analyses utilizing only two to four studies. The majority of the studies compared cognitive scores to the patients themselves and not to a control group, and the majority of studies compared types of ECT modalities (electrode placement, etc) rather than having a true control group for comparison.

c. Regarding long term executive function after ECT, FDA concedes, "There is limited long-term data on executive function. Therefore, no meaningful conclusions can be drawn."

d. Regarding disorientation after ECT, FDA states,"There is no evidence that disorientation following ECT is long-term or persistent." The wording of this FDA statement is deceptive and appears to imply that studies have not found persistent disorientation. In fact as FDA admitted, long term studies have not been done.

e. Regarding global memory function immediately after ECT, in the sub acute period, in the medium term, and at 6 months, FDA notes that the evidence is "limited" or "equivocal".

f. Regarding anterograde verbal memory, FDA notes that the data is "limited" and "equivocal".

g. Regarding anterograde nonverbal memory, FDA cites there is data that ECT is associated with more decline immediately post-treatment than sham ECT, but then makes a contradictory statement that, "There does not appear to be any change from baseline." This inconsistency is a reflection of the contradictions in the selected inadequate medical literature. Regarding sub acute and changes and changes 2 weeks post ECT, FDA states the data is "equivocal" and lacks conclusive evidence, respectively, again affirming the inadequacy of the existing studies.

h. Regarding retrograde impersonal memory, FDA states, "There are no studies reporting retrograde impersonal memory data from three to less than six months following ECT." The selected studies that addresses retrograde impersonal memory 6 months post ECT include small subject populations utilizing different measurement instruments, and therefore are not legitimately combined.

i. Regarding retrograde personal (autobiographical) memory, FDA selected inadequate studies. Their summary of the studies of autobiographical memory loss at various post-treatment intervals is at times is exceedingly misleading, contradictory, and highly qualified (data is repeatedly characterized as "limited" or "equivocal").

i. FDA considered analyses which largely consisted of comparing different ECT modalities. Only a minority of subjects were compared to actual non-ECT controls or to sham ECT. It is not legitimate to summarize the conclusions from this diverse treatment population.

ii. The largest single study cited in this section (Weiner et al, 1986) examined 74 subjects. The majority of the comparisons were among the differing ECT modalities. The majority of the memory tests were not for personal memory. There was a statistically significant decline in personal memory persisting at 6 months. This is grossly misrepresented in the executive summary report on page 30, where there is only mention of improvement from the 3-month memory deficits. Although clearly indicated in the appendix, FDA executive summary fails to identify the major outcome of this study, which was that significant personal (autobiographical) memory deficits persisted at 6 months.

iii. FDA conceded "the importance of ECT effect on autobiographical memory" and therefore they ran additional analyses. The selected studies did not meet FDA's criteria of Randomized Controlled Studies (RCTs); instead they were nonrandomized and did not compare to control subjects. They were also very short term, with two studies measuring memory at 1-3 days post treatment, five studies reporting one-week post treatment memory, two studies reporting at one month and one study post-course. There was only one study which tested for personal memory at 6 months, and that was the aforementioned (Weiner, 1986) which documented statistically significant persistent personal memory loss. The selected studies are referred to in Table 7 of the appendix, which is falsely entitled "Autobiographical Memory – RCTs Reporting Change from Baseline Data".

j. FDA largely dismisses subjective memory loss (self-reported complaints).

k. The FDA Executive Summary regarding cognitive adverse events is replete with a primary contradiction: The evidence for treatment-related deficits in various kinds of cognitive functions, especially memory, is summarized as limited, equivocal, or lacking, Yet, the evidence comparing adverse cognitive effects between various ECT modalities routinely describes greater or lesser deficits for one modality versus the other. FDA fails to explain the consistent finding of adverse effects when comparing ECT modalities but the relative lack of conclusive evidence for adverse effects when compared to a true control group not receiving ECT.

14. FDA only gives a cursory address to neuropathological and immunohistochemical evidence of brain damage. Two paragraphs simply highlight the contradictory evidence, from which no rational conclusion is valid.

a. FDA cites two papers from one researcher to conclude that there are not histopathological or cellular changes in brain tissue. Without acknowledging the contradiction, FDA admits to definite electroshock-induced neuroproliferative changes seen in other studies.

b. In the next paragraph FDA mentions the finding of no brain cell death associated with electroshock. However FDA admits definite brain cell loss due to electroshock in three other studies.

c. Furthermore, FDA endorses the idea that electroshock-induced neuroproliferation could be a therapeutic effect, without mentioning that this is not a widely held theory. In fact, studies omitted from review by FDA documented that electroshock-induced neuroproliferation is typical of the neuroproliferative response to other forms of brain injury. New brain cells do not integrate into existing brain structure in a normal pattern. After an electric shock, existing brain cells exhibit persistently abnormal conduction of electricity (Scott, et al, 2000; Gombos, et al, 1999). This is explained by the finding that synapses on such new brain cells have deranged structure, and are positioned along the nerve in atypical locations compared to normal brain cells (Chen, et al, 2009).

15. Neuroimaging evidence of brain changes are dismissed by citing Coffey et al. (1991) and Ende et al. (2000), both of which are misrepresented by the FDA summary.

a. The cited study by Coffey et al, looked at the MRI brain scans of patients before and after ECT. Out of 35 patients studied, 8 had new changes on MRI after shock. 22%, or greater than one in 5, sustained anatomic brain effects. Among those with the brain changes, one patient suffered a stroke and two had new abnormal neurologic signs on exam within 6 months of the ECT.

b. In the cited study by Ende, et al, brain scans demonstrated a 16% decrease in choline in the hippocampal region, attributed by the authors to" membrane turnover". Membrane turnover is a direct indicator of cell wall damage.

16. The narrow literature selection by FDA could easily be considered as some evidence that ECT does not increase biomarkers of brain damage. However the selection inexplicably ignores the much larger body of literature that substantiates the opposite conclusion: there is abundant evidence that ECT does in fact lead to a brain inflammatory response, brain cell leakage, neuronal damage and BBB dysfunction.

a. Blood levels of S-100b are 2X to 8X higher after electroshock. S-100b is a brain biochemical that is an irrefutable marker of brain damage when it is detected to rise in the bloodstream (Palmio, et al, 2010).

b. Gene expression of proteins relating to apoptosis is diminished after electroshock. This results in the blunting of normal programmed cell death in the brain; thus defective or aging cells do not undergo normal removal, but stay in place and continue to function in a faulty way (Jeon, et al, 2008).

c. Mitochondrial enzyme levels change with electroshock, particularly decreasing levels of one key regulating enzyme (Burigo, et al, 2006).

d. Biochemical damage of brain cells from electroshock has been demonstrated by the finding that brain genetic material is subsequently more accessible to chemotherapy toxins (Salford, et al, 2000).

17. Regarding mortality associated with ECT, FDA maintains a double standard for sufficiency of evidence.

a. FDA mentions "a number of observational and epidemiological studies [that] have examined the rate of mortality associated with ECT". In fact, such studies identified a significantly higher mortality compared to depressed subjects not subjected to ECT. FDA concluded that there insufficient studies on the reduced life span associated with ECT.

b. FDA describes the death estimate of 1 in 10,000 mentioned in the 2001 APA practice guideline. The figure given in the practice guideline was never based on any study, and the source of the estimate remains a mystery. Thus this does not qualify as evidence.

c. FDA cites Watts, et al (2010) to indicate a death rate 800% lower than the APA estimate. This was a Veteran's Administration study based on in-hospital only deaths specifically reported as ECT related to the VA's National Center for Patient Safety (NCPS) database. The NCPS has never been verified to be a statistically reliable repository of cause-of-death data. A review of medical charts to independently ascertain the precipitating causes of death was not undertaken.

d. FDA cites two studies by Kramer (1985; 1999) regarding extrapolated death rates associated with ECT in California. Like the VA study, the death registries in the Kramer studies were not verified by medical record review to independently ascertain the precipitating causes of death.

e. The significance of the lack of independent verification of ECT-related causes of death is suggested by the attempts to verify cause-of-death data in other types of registries. For example, incorrect assignment of cause of death has been responsible for large inaccuracies in databases for cardiovascular deaths (Harriss, 2011), pregnancy associated deaths (MacKay, et all, 2011), fetal deaths and stillbirths (Makelarski, et al, 2011), kidney disease (Pun, et al, 2011), AIDS (Trepka, 2011) and cancer (Polednak, 2011).

f. Studies excluded from consideration by FDA demonstrate increased mortality.

i. The largest study ever conducted of ECT recipients involved 3,288 patients in Monroe County, NY. ECT patients were found to have significantly increased death rates from all causes (Babigian, et al, 1984).

ii. A study of 37 patients who received in-hospital ECT had survival rates of 73.0% at one year, 54.1% at two years, and 51.4% at three years. In contrast, depressed patients who

did not receive ECT had survival rates of 96.4%, 90.5% and 75.0% at 1, 2 and 3 years respectively (Kroessler and Fogel, 1993).

iii. The first three years of mandated recording of death within 14 days of ECT in the state of Texas yielded reports of 21 deaths. Eleven of these were cardiovascular, including massive heart attacks and strokes, three were respiratory deaths and six were suicides (Gilbert, 1996). Many of these were not sustained while the patient was in the hospital and would not be expected to be captured as ECT related in the absence of an independent review of the medical records.

Conclusions regarding review of the medical literature on SAFETY of ECT

The FDA Executive Summary (Draft) admits to inadequate medical literature, insufficient measuring tools, wide variability of results, lack of adequately populated randomized controlled trials, and virtually nonexistent long term studies.

FDA broadly discounts observational studies when the result support an ECT adverse effect (such as death and suicidality) but include observational studies in which ECT appears less treacherous.

FDA violates its own stated standards by including non randomized, uncontrolled studies, yet invoking its standards to eliminate from consideration hundreds of other studies.

FDA relies on review articles and meta-analyses that overlap, and include mostly small, short term, studies with incompatible measuring tools. The insufficient literature is then inappropriately combined in unsubstantiated conclusions. This includes several instances of misrepresentation of the original studies.

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EXHIBIT 3

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February 8, 2012

Daniel R. Levinson
Inspector General
U.S. Department of Health & Human Services
PO Box 23489
Washington, DC 20026

Complaint of Misconduct
Center for Medical Devices and Radiological Health,
Food and Drug Administration

Dear Mr. Levinson:

On January 27 and 28, 2011, the FDA held hearings of the Medical Devices Advisory Committee, Neurological Devices Panel, regarding the potential declassification of Electroconvulsive therapy ("ECT") devices from device Class III to device Class II. I provided testimony at the hearings based on my substantial experience arising from litigation on behalf of ECT victims.

For more than 35 years, ECT devices have been categorized as Class III – the most dangerous device category – and the FDA had never required the manufacturers to prove that ECT treatments were either safe or effective.

At the hearings, some Advisory Committee Panel members queried FDA representatives on the procedure the FDA would follow if the Panel recommended the devices remain in Class III. They were informed that the ECT device manufacturers would have to submit a "Pre-Market Approval application" ("PMA"), to *prove* the safety and efficacy of the devices through clinical trials.

I have recently spoken to FDA official, Lt. Commander Bradley Cunningham, who was present at the hearings as a representative of the FDA, and who has a supervisory position with respect to the determination of whether ECT devices would be placed in Class II or Class III, and whether the manufacturers would be required to submit PMAs. LCDR Cunningham informed me of several alarming potential positions of the FDA.

Although the Advisory Committee Panel voted to retain Class III for all uses of ECT but for "catatonia," LCDR Cunningham expressed that the FDA is also considering changing the classification of ECT devices to Class II for "treatment resistant depression." I told him that the Panel had voted that the use of these devices for depression should remain in Class III, but he responded that the Panel should not have voted *at all*, and inferred the FDA could disregard the vote.

LCDR Cunningham also acknowledged that if there is ultimately a "split" classification – some uses denominated in Class II and some uses Class III -- then doctors would be free to treat the device as Class II based upon doctor's discretion for any potential usage. Yet, he also acknowledged that such discretionary use would be a matter outside of the FDA's control, and, by inference, not the FDA's problem.

Indeed, that is exactly what occurs with the use of many medications, such as the antipsychotic drug Zyprexa, which was FDA approved for treatment of certain conditions, but doctors prescribe it for myriad unapproved purposes, including giving to children. Allowing such "doctor discretion" caused improper sales of over a billion dollars.

Moreover, what may constitute "treatment resistant" depression is subject to guess work, speculation and whim. Arbitrary or biased criteria for using ECT would open the door to massive abuses we have similarly seen with antipsychotics and antidepressants.

Second, according to LCDR Cunningham, if the manufacturers are required to submit a PMA, the FDA is considering allowing them to submit "paper PMAs," which means the manufacturers could submit prior published studies to meet what is supposed to be a rigorous standard of *proof*. Yet, in over 30 years, the manufacturers have failed to provide any clinical studies to warrant ECT's use and, in fact, the Advisory Panel clearly recognized that the existing studies failed to clearly demonstrate safety of the devices.

This highly unusual "paper PMA" procedure is based on the assumption that the manufacturers may have inadequate financial resources to conduct clinical trials. In essence, the FDA would give the manufacturers of these devices an exemption for the demonstration of clinical *proof* of safety and efficacy of the devices out of sympathy for the manufacturers' finances. This belittles the harm to

patients, puts corporate financial concerns above patient care, and fails in the FDA's sworn duty to protect the public.

Moreover, the FDA's own Executive Summary on the ECT device prepared before the 2011 hearings, [1] noted that, (even with the limited and hand-picked group of studies the FDA chose to consider, as addressed below), "A long-standing safety concern with the use of ECT is the potentially detrimental effect on memory and other cognitive functions. *Published studies have yielded mixed and confounding results.*" (Executive Summary, p. 21.)(emphasis added)

Third, when I reminded LCDR Cunningham that the public docket in this case manifested an extraordinary amount of opposition to declassification, including literally thousands of statements from persons asserting they or loved ones had been harmed by ECT, he denigrated such statements as "anecdotal," and which were, he inferred, insignificant to the FDA's decision.

Yet, the FDA's Executive Summary of research regarding ECT conceded there was massive opposition to declassification and that many persons reported serious injuries from ECT. These, the FDA has chosen to categorize as merely "anecdotal." The Executive Summary stated:

> A majority of respondents, 79%, expressed an opinion against reclassification (i.e., maintain Class III designation) while 14% supported reclassification (i.e., reclassify to Class II). In addition, there were 92 group submissions, representing a total of 6462 individuals, against reclassification and 462 individuals in favor of reclassification. A majority of respondents identified an adverse event they felt was associated with ECT treatment. The most common type of adverse event reported in the public docket was memory adverse event (529 reports). This was followed by other cognitive complaint (413 reports), brain damage (298 reports) and death (103 reports).

(Executive Summary, p. 14.)

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[1] "FDA Executive Summary, Prepared for the January 27-28, 2011 meeting of the Neurological Devices Panel, Meeting to Discuss the Classification of Electrotherapy Devices (ECT)"

Exclusion of death, mayhem and destruction of memory as "anecdotal" is aggravated by the FDA's exclusion in its Executive Summary of many published studies that have established such harms as ubiquitous in the practice of ECT. In choosing what published studies to consider in its evaluations, the FDA excluded more than 94% of all studies relating to ECT, because the excluded studies allegedly did not meet its criteria for the level of scientific rigor. It thus included for serious evaluation only 68 studies published in the past 70 years regarding ECT and excluded 1163 studies. Many of the excluded studies found that ECT lacked efficacy and/or unquestionably created severe and permanent harm to patients. (Executive Summary, p. 12.)

In short, notwithstanding the vast number of persons and entities submitting comments that opposed declassification, notwithstanding the FDA's recognition of the extensive harm from ECT consumers they and their families have reported, notwithstanding that even the FDA concedes that its selected studies are, at best, "confounding" in terms of the long term harms of ECT, the FDA is willing to permit the manufacturers to *avoid* the submission of a proper clinical PMA. The FDA is seriously considering that the manufacturers can continue to market and sell this device without demonstrating whether or not it can muster clinical proof of either safety or efficacy.

If this happens, the decision will be based in substantial part upon concern for the manufacturer's finances rather than the health and safety of patients. Worse, the decision to avoid a PMA and to issue unprecedented "split" classification would be made despite recognition that doctors would be free then to use the device as if it were Class II for essentially any reason.

Such a result would be very irresponsible for an agency sworn to protect the health and safety of citizens, and would manifest that the FDA has other goals and interests in mind. I request this matter be investigated.

Sincerely,

Kendrick Moxon

cc: Margaret Hamburg, M.D.
Commissioner, FDA

Jeffrey E. Shuren, M.D., J.D.
Director, Center for Medical Devices
and Radiological Health

EXHIBIT 4

Hindawi Publishing Corporation
Case Reports in Psychiatry
Volume 2012, Article ID 585303, 4 pages
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Case Report

Subdural Hematoma: An Adverse Event of Electroconvulsive Therapy—Case Report and Literature Review

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Electroconvulsive therapy (ECT) is commonly used in the management of medication nonresponsive depressive disorder, with proven efficacy in psychiatric practice since many decades. A rare complication of intracranial bleed following this therapeutic procedure has been reported in sporadic case reports in the English literature. We report a case of such a complication in a 42-year-old male, a known case of nonorganic medication nonresponsive depressive disorder for the last two years who required ECT application. Presenting symptoms included altered mental state, urinary incontinence, and repeated episodes of vomiting; following ECT procedure with magnetic resonance imaging (MRI) of the brain suggestive of bilateral acute subdural hematoma. Despite the view that it may be used in neurological conditions without raised intracranial tension, it will be worthwhile to be vigilant during post-ECT recovery for any emergent complications.

1. Introduction

Electroconvulsive therapy (ECT) is a treatment modality in which electricity is used to create a seizure in a patient who has received general anaesthesia. ECT is most commonly used to treat depressive disorder and has been shown to be effective for many such patients with suicidal ideations, as also they do not respond to medication trials or psychotherapies [1, 2]. Recently two case reports of chronic subdural haematoma following modified ECT were described [3, 4]. Surprisingly, another case report of bipolar disorder with traumatic acute subdural hematoma being treated with series of ECT a week following cranioplasty is also known [5]. Recent large outcome studies have reported no cases of cerebral haemorrhage [6, 7]; nevertheless emerging case reports in the past decade may notify some of the rarest complications associated with modified ECT, cause for which remains obscure. In spite of the frequent usage of ECT only few serious complications have been reported in the English literature [3, 4, 8]. This is particularly true of the intracranial bleed, which is sporadically described and reported.

2. Case Report

A 42-year-old married adult male with right hand dominance, from urban and upper socioeconomic background presented with gradual onset, nonprogressive, pervasive depressed mood of two-year duration with symptoms of insomnia, anorexia, lack of interest and enjoyment, and ideas of worthlessness, hopelessness, and helplessness, leading to socioоccupational dysfunction. He also presented with suicidal ideations of two-week duration, with Hamilton Depression Rating Scale 17-item (HAMD-17) [9] score of 25 (very severe depression) at the time of admission. He was diagnosed as having chronic depressive disorder as per ICD-10 diagnostic criteria [10]. He had been on treatment for a year from a psychiatrist on escitalopram (20 mg/day), mirtazapine (45 mg/day) and clonazepam (0.5 mg/day), but showed no significant clinical improvement. He had no prior medical history of hypertension, diabetes mellitus, fall/head injury or anticoagulant/antiplatelet drug intake, bleeding diatheses, renal problems, epilepsy, or alcoholism. Patient had cordial family and work atmosphere with no

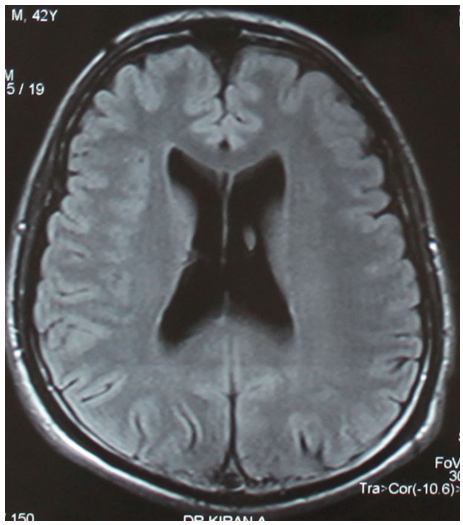

Figure 1: Pre-ECT cranial magnetic resonance imaging with contrast done to rule out organic causes of depression showing normal study.

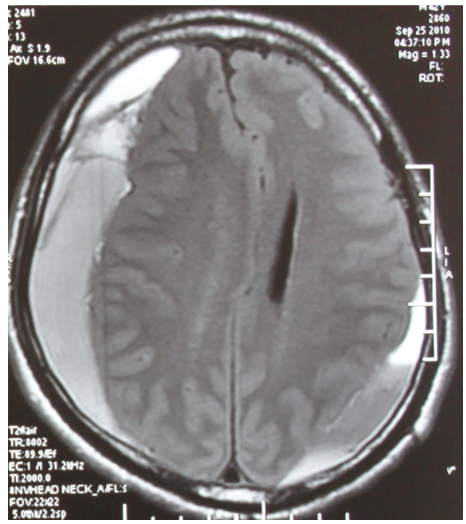

Figure 2: Post-ECT cranial noncontrast magnetic resonance imaging showing bilateral asymmetric extensive acute subdural hematoma extending over right frontoparietal and left parietal areas with mass effect and midline shift to left.

family history of psychiatric illnesses. His vital parameters, physical examination, fundoscopy, and neurological opinion revealed none of the problems which can be attributed to organic brain pathology. Biochemical and haematological investigations like blood glucose, coagulation profile, liver function tests, thyroid profile, and complete blood counts were within normal limits.

In view of presence of chronic severe depression with recent suicidal ideations, poor response to treatment with antidepressants, and absence of psychosocial stressors, patient underwent magnetic resonance imaging (MRI) brain screening to rule out organic causes for depression (Figure 1), prior to the consideration of ECT. Standard protocol as prescribed by the Royal College of Psychiatrists for ECT was followed [11]. Written informed consent for the procedure was taken from the patient and caregiver. His vital parameters were 124/80 mm of Hg of blood pressure with pulse rate of 80 beats per minute. During the first sitting of modified ECT, patient received 0.6 mg glycopyrrolate, 80 mg propofol, and 50 mg succinyl choline. ECT was delivered using standard brief pulse ECT machine with bitemporal electrode placement and delivery of brief pulse waveform electrical stimulus strength of 120 mC dosage, 1.5 msec pulse width, 800 mA pulse amplitude, and 125 pulse per second for duration of 1.2 seconds resulting in an adequate motor seizure duration of 47 seconds. During ECT procedure, patient had rise in blood pressure to 158/96 mm of Hg with pulse rate of 110 beats per minute, without return to normal values after the procedure. Post-ECT recovery was delayed as patient had altered mental state, repeated episodes of vomiting and bladder incontinence with Glasgow Coma Scale (GCS) [12] score of E2 M2 V4 at the end of one hour after ECT. Bilateral pupils were middilated but reactive to light. His fundoscopy showed papilledema suggestive of raised intracranial tension. Patient did not sustain any fall or head injury prior to, during, or soon after the procedure.

A cranial MRI reported bilateral asymmetric (right more than left side) extensive acute subdural hematoma over right frontoparietal and left parietal areas with mass effect and midline shift to left side (Figure 2). Overlying bone window was normal. Patient underwent an emergency neurosurgical intervention, and hematoma was evacuated with burr-hole operation. All psychiatric medications were discontinued until surgically stabilized. After 24 hours of evacuation, patient had Mini-Mental Status Examination (MMSE) [13] score of 28 out of 30, and GCS score improved to E4 M6 V5. After 72 hours, patient's condition deteriorated due to the recollection of bilateral acute on subacute subdural hematoma with mass effect, confirmed by cranial MRI study. Neurosurgical reexploration and reevacuation stabilized the patient's condition without any further recollection of blood in subdural space. A week later, patient had moderate depression without suicidal ideations, with a significant decrease in HAMD-17 item scores from preoperative score of 25 to 14. Escitalopram was not considered in view of risk of bleeding with selective-serotonin reuptake inhibitors, and the patient was discharged with mirtazapine (15 mg/day). On subsequent followup, patient showed improvement with mirtazapine (30 mg/day).

3. Discussion

ECT is an accepted treatment modality for severe psychiatric illnesses since many decades. It is considered as an effective treatment for medication nonresponsive severe depressive disorder and a life-saving therapeutic procedure in those with suicidal ideations as was the case in our patient. Risks and adverse events of ECT can be divided into two categories: firstly, those medical complications that can be substantially reduced by the use of appropriately trained staff, best equipment, and best methods of administration;

secondly, those side effects, such as transient posttreatment confusion, headache, and spotty but persistent memory loss that can be expected even when an optimal treatment approach is used. In the recent series reported, there were 2.9 deaths per 10000 patients; another series reported 4.5 deaths per 100000 treatments. Overall, the risk is not different from that associated with the use of short-acting barbiturate anaesthetics. In another study of almost 25000 treatments, a complication rate of 1 per 1300 to 1400 treatments was found [2]. These included laryngospasm, circulatory insufficiency, tooth damage, vertebral compression fractures, status epilepticus, peripheral nerve palsy, skin burns, and prolonged apnea. The time it takes to recover clear consciousness may vary from minutes to several hours, depending on individual differences in response, the type of ECT administration, the anaesthetic substance utilised, the spacing and number of treatments given, and the age of the patient [2]. Advanced medical technology has substantially reduced the complications associated with ECT.

Intracranial parenchymal bleeds form an important subgroup of extremely serious although very rare complication, which has been scantily reported following modified ECT. It is particularly difficult to establish the iatrogenic cause of intracranial bleed. Nevertheless, the true incidence of intracranial bleeds after ECT seems to be underestimated. However, cases of neurological insults such as subdural bleed were not found to increase or deteriorate during an ECT with observed safety in these patients [14, 15]. In patients with neurological abnormality after ECT, it may be more difficult than usual to diagnose an intracranial insult such as intracranial bleed. However, any persistent change in the level of sensorium, additional focal neurological signs, epileptic convulsions, repeated episodes of vomiting, and incontinence in patient receiving ECT should arise a highest degree of suspicion of intracranial adverse events that justify the need for neuroimaging investigations. Computed tomography (CT) or MRI scans are valuable in diagnosing and localising intracranial insults as was in our case. Awareness of possibility of such potential adverse event among treating psychiatrists, after ECT and in followup of a case having undergone ECT, results in lifesaving of such patients.

Acute, rapidly evolving subdural hematomas are due to tearing of bridging pial veins, and symptoms are caused by compression of the brain by an expanding clot of fresh blood. ECT has been administered in psychiatric patients with neurological conditions without raised intracranial tension, including postcraniotomy, cranioplasty, subdural hematomas, and brain tumours in the literature [5]. In our case, acute subdural hematoma presented in temporal association with ECT and hence possibly could be secondary to ECT. The exact mechanism of such causation remains obscure. However, possible explanations for this rare complication are put forth. Firstly, anterior communicating artery or MCA bifurcation berry aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect [16]. Secondly, subdural hematoma can also result as a potentially serious consequence of spontaneous intracranial hypotension (SIH) with reported incidence of 10% [17, 18]. The diagnosis of SIH should be considered in patients presenting with subdural hematoma in the absence of trauma and with normal clotting, particularly as subdural hematomas secondary to intracranial hypotension may recur following drainage, and treatment of the underlying cause is required [19].

It must be noted that hyperventilation done prior to ECT reduces CSF pressure and may therefore contribute to the reduction in intracranial pressure. In general it can be stated that changes in cerebral blood flow always induce changes in the cerebral blood pressure in the same direction. Certain cases of arteriosclerosis with decreased cerebral blood flow show reduced CSF pressure, which may reflect the reduction in size of the intracranial vascular bed. The reduced intracranial circulation may also curtail CSF production and lead to intracranial hypotension [20].

4. Conclusion

Application of ECT, although a proven efficacious and safe therapeutic procedure in psychiatric practice since many decades, should be administered and monitored during and after each treatment for any adverse event. A cranial CT or MRI may be done in suspected organic causes of psychiatric disorders to rule out any intracranial pathology before considering ECT, especially in cases of refractory depression. Despite the view that it may be used in severe psychiatric illnesses with neurological conditions without raised intracranial tension [5], recent case reports of chronic subdural haematoma following modified ECT [3, 4] emphasize the need to be vigilant, especially in case of delayed recovery, persistent delirium, or signs of organicity (altered sensorium, vomiting, and incontinence) following ECT for any emergent complications such as subdural hematoma.

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