No. 21-55517

S273887

*In the*

# United States Court of Appeals

*for the*

# Ninth Circuit

MICHELLE HIMES; MARCIA BENJAMIN; and DANIEL BENJAMIN;

*Plaintiffs-Appellants,*

vs.

SOMATICS, LLC,

*Defendant-Respondent.*

Appeal from an Order of the United State District Court for the Central District of California, Case No. 2:17-cv-06686-RGK- JCx
Hon. R. Gary Klausner

**APPELLANTS' EXCERPTS OF RECORD**
**VOLUME 4 OF 6**

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**G1-10 to G1-2000 10 - 2,000 UV/cm in 7 steps**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "CHANN 1" is displayed.**
3. **Press the *FlexDial*™ to see a flashing display of the present channel 1 gain setting ("G1-OFF" to "G1-2000").**
4. **If the number you want is flashing, just press the START/STOP button to retain the setting and proceed to the next variable, which is the channel 1 *POSITION* setting.**
5. **Otherwise, rotate the *FlexDial*™ left or right until the setting you want is flashing in the display.**
6. **Press the *FlexDial*™ to select and save the setting and proceed to the next variable, which is the channel 1 *POSITION* setting.**

**Or,**

7. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode**

**(*NOTE*: POSITION is *always* set following GAIN, because positioning of the tracing on the recording paper depends on the amplitude, or GAIN, of the signal. Thus, it is always necessary to set the GAIN in a specific channel before setting the POSITION, as noted in step #5 in the immediately preceding paragraph).**

**The choices for *position* are as follows:**

| | |
|---|---|
| **P1-AUTO** | **Selects auto-positioning of recording trace** |
| **P1-0 to P1-800** | **Adjusts position on strip from 0 (bottom) to 800 (top).** |

1. **After setting channel 1 GAIN as described above, "P1-AUTO" will flash in the display.**
2. **Press the *FlexDial*™ to select auto-positioning of the recording trace (recommended unless a problem is experienced with crowding of the traces on the paper).**
3. **Alternately, rotate the *FlexDial*™ to see a flashing display of the remaining channel 1 POSITION choices.**
4. **Press the *FlexDial*™ to select and save your choice and return to the channel 1 entry point, in order to set GAIN or POSITION for channels 2, 3, and 4**

**Or,**

7. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode.**

**If you have chosen to return to the channel 1 entry point in order to set GAIN and POSITION for channels 2, 3, or 4, you will now see "CHANN 1" in the display again.**

***Rotate the FlexDial*™ *to the right* to display CHANN 2, CHANN 3, or CHANN 4 in the L.E.D., and proceed as described above for channel 1 to set GAIN or POSITION for any or all of the other recording channels.**

**SEIZURE QUALITY MEASURES**

**The Thymatron™ System IV provides 6 *Seizure Quality Measures* that can be individually enabled/disabled. Their names and *FlexDial*™ designations are as follows:**

| | |
|---|---|
| ***Seizure Energy Index*** | **SEI ON/OFF** |
| ***Postictal Suppression Index*** | **PSI ON/OFF** |
| ***Seizure Generalization Index*** | **SGI ON/OFF** |
| ***Maximum Sustained Powere and Time to Peak Power*** | **MSP ON/OFF** |
| ***Maximum Sustained Coherence and Time to Peak Coherence*** | **COH ON/OFF** |
| ***Duke University Amplitude Measures*** | **DUKE ON/OFF** |

**The *FlexDial*™ procedure for selecting each of these measures is similar. Following is the procedure for enabling the *Seizure Energy Index*.**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "INDEXES" is displayed.**
3. **Press the *FlexDial*™ to see a flashing display of the status of the Seizure Energy Index program ("SEI ON" or "SEI OFF").**
4. **If "SEI ON" is flashing, just press the START/STOP button to retain the setting and exit *FlexDial*™ mode ("READY" will appear in the display if a baseline EEG has already been collected; otherwise, "NO BASE" will appear).**
5. **If "SEI OFF" is flashing, rotate the *FlexDial*™ left or right until "SEI ON" is flashing in the display.**
6. **Press the *FlexDial*™ to select and save the setting and proceed to selection of the next variable (*Postictal Suppression Index, PSI*)**

**Or,**

7. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode**

***NOTE*: From the INDEXES entry point, repeatedly pressing the *FlexDial*™ will show a sequential flashing display of the status ("ON" or "OFF") of the SEI, PSI, SGI, MSP, COH, and DUKE, in that order. Turning the dial left or right at each flashing display allows the user to enable or disable each index as desired (and proceed to the next index) by pressing the *FlexDial*™. When the last of the indexes (DUKE) is enabled/disabled by pressing the *FlexDial*™, the display returns to INDEXES once again.**

**TO SET PAPER (CHART DRIVE) SPEED, OR TURN CHART DRIVE OFF**

**The choices are:**

| | |
|---|---|
| **PRINT 5** | **5 mm/sec** |
| **PRINT 25** | **25 mm/sec (*as shipped)*** |
| **PRINT 50** | **50 mm/sec** |
| **PRINTOFF** | **Disables printing of monitoring traces (EEG, ECG, EMG)** |

**The Thymatron™ System IV is shipped with the paper speed set to 25 mm/sec. Alternate paper speeds of 5 mm/sec and 50 mm/sec may be selected, *or the printing of the monitoring traces turned off entirely,* as follows**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "PRINTOUT" is displayed.**
3. **Press the *FlexDial*™ to see a flashing display of the present paper speed setting**
4. **If the desired paper speed setting is flashing, just press the START/STOP button to retain the setting and exit *FlexDial*™ mode ("READY" will appear in the display if a baseline EEG has already been collected; otherwise, "NO BASE" will appear).**
5. **Otherwise, rotate the *FlexDial*™ left or right until the desired paper speed setting is flashing in the display.**
6. **Press the *FlexDial*™ to select and save the setting and proceed to selection of the next variable (*FFT ON/OFF*)**

**Or,**

7. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode**

## TO TURN OFF THE PRINTOUT OF THE POWER SPECTRAL ANALYSIS

**The Thymatron™ System IV is shipped with the power spectral analysis printout enabled; to disable this feature:**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "PRINTOUT" is displayed.**
3. **Press the *FlexDial*™ twice to advance through the paper speed choices and see a flashing display of the present status of the power spectral analysis printout function ("FFT ON" or "FFT OFF").**
4. **Rotate the *FlexDial*™ left or right until "FFT OFF" is flashing in the display.**
5. **Press the *FlexDial*™ to select and save the setting and return to the PRINTOUT entry level.**

**Or,**

6. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode**

**TO SAVE USER-SPECIFIED CONFIGURATIONS OF ALL FLEXDIAL™ SETTINGS**

**Choices:**

**SAVE-US1 through SAVE-US8**
**CANCEL**

**This feature is used to store up to a total of 8 user-specified FlexDial™ configurations in memory (e.g., up to 8 individual doctors' personally-preferred settings for *all* the FLEXDIAL variables; up to 8 special-purpose FlexDial™ configurations, etc.) After they have been set, these user-specified configurations can be selected from the "SETTING" location of the *FlexDial*™ shell: "SET US1" through "SET US8".**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "SAVE USR" is displayed.**
3. **Press the *FlexDial*™ to see a flashing display of the first of the 8 possible bins for storing user-specified configurations: "SAVE-US1". Turn the *FlexDial*™ left or right to see the remaining possible storage bins ("SAVE-US2 through "SAVE-US8").**
4. **Display the storage bin you wish to use for all present *FlexDial*™ settings (e.g., "US-1") and press the *FlexDial*™ to store in memory and return to the SAVE SET entry level. *[WARNING: All previously set FlexDial™ values in that bin will be erased!]***

**Or,**

6. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode**

**TO SELECT USER-SPECIFIED CONFIGURATIONS OF ALL FLEXDIAL™ SETTINGS**

**Choices:**

**SET-US1 through SET-US8**
**RESET**
**CANCEL**

**This feature is used to select one of up to 8 previously-saved user-specified FlexDial™ configurations from memory (see previous paragraph), or to RESET the Thymatron System IV to the factory-set (*DEFAULT*) values.**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "SETTING" is displayed.**

3. **Press the *FlexDial*™; "RESET" will flash in the display. Turn the dial to the right to see a flashing display of the first of up to 8 possible user-specified FlexDial™ configurations: "SET-US1". Keep turning the *FlexDial*™ to see the remaining user-specified *programs [NOTE: Numbers are assigned only if programs have been saved—you will not necessarily find 8 programs stored in memory]***
4. **Display the program you wish to use (e.g., SET-US1") and press the *FlexDial*™ to select it and return to the "SETTING" level.**

**Or,**

5. **Press the START/STOP button on the front panel to select and save setting and exit *FlexDial*™ mode.**
6. ***Alternatively, turn the dial to "RESET" if you wish to reset the unit to the DEFAULT settings (or to "CANCEL" if you change your mind and want to exit the program unchanged )***

## TO INPUT TREATMENT DATA PREVIOUSLY COLLECTED WITH THE THYMATRON™ SYSTEM IV AND STORED IN A PC

**The Thymatron™ System IV allows the operator to download previously-stored treatment data from a personal computer file back into the Thymatron™ System IV, when the PC has been properly set up with the correct software. The procedure is as follows (the treatment data must already have been collected with the Thymatron™ System IV and uploaded to a PC using the DATA OUT utility of the Thymatron™ System IV):**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial until "DATA IN" is displayed.**
3. **Press the dial once; "DATA IN" will begin flashing. Now is the time to connect the PC to the rear-panel RS232 (serial) port.**
4. **Press the dial again; "IN ←" will start to flash in the display. Now is the time to initiate data transfer from the PC.**
5. **Data transfer is complete when the display stops flashing. Press the *FlexDial*™ or START/STOP button to return to the DATA IN level.**

## TO SELECT DATA OUTPUTTING OPTIONS

**The Thymatron™ System IV allows the operator several options for outputting the data of the treatment just given, as follows:**

**REPRINT Directs the Thymatron™ System IV to print a complete strip of the treatment just given, whether or not an end-of-treatment report has already been printed**

**(NOTE: *The following choices require the GENIE™ software to be installed on a PC and connected to the Thymatron™ System IV as desribed in the Appendix below. It is also possible to use a PC that has been set up to receive data with a suitable commercially-available program, such as the modem program "Procomm".)***

**RAW DATA** **Sends the digitized EEG data, including all FFT points and EEG indices, through the serial port to a PC.**

**FFT DATA** **Sends all FFT points and EEG indices through the serial port to a PC.**

**RESULTS** **Sends ASCII files of treatment results through the serial port to a PC.**

**EXIT** **Returns to the FLEXDIAL shell**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "DATA OUT" is displayed.**
3. **Press the *FlexDial*™; "REPRINT" will flash. Rotate the *FlexDial*™ to display the alternate choices listed above.**
4. **When your choice is flashing in the display (e.g., "RAW DATA") , press the *FlexDial*™ to initiate printing or data output, according to your selection. *[NOTE: If no treatment data is stored in memory the message "EMPTY" will flash and no data transfer will occur]***
5. **To EXIT and return to DATA OUT, turn the dial until "EXIT" is flashing and press the dial,**

**or,**

6. **Press the START/STOP button to exit the *FlexDial*™ shell.**

**TO SET DATE & TIME IN PRINTED REPORT**

**The FlexDial™ "CLOCK" mode choices are as follows:**

**MONTH** **01 - 12**

**DAY** **01 - 31**

**YEAR** **00 - 99**

**HOUR** **00 - 24**

**MIN** **00 - 60**

**Each choice is selected and set by the same general procedure—the following example for setting the *month* is used to set all the CLOCK variables:**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., "SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "CLOCK" is displayed.**
3. **Press the set button to display "MONTH xx".**
4. **Rotate the dial to display the desired month (e.g., "MONTH 06")**
5. **Press the dial again to select and save your choice and advance to "DAY xx"; repeat as desired to set the *day, year, hour* and *minute*, in sequence,**

**or,**

6. **Press the START/STOP button to save your settings and exit the *FlexDial*™ mode.**

*[Appendix]*

# GENIE™ IV MANUAL

## COMPUTER-ASSISTED EEG ANALYSIS SOFTWARE FOR THYMATRON™ SYSTEM IV

**(WINDOWS 95-98)**

**John Pavel**

**&**

**Richard Abrams, M.D.**

## DESCRIPTION

**The Genie™ IV 4-channel computer-assisted EEG analyzer-analyzer is an accessory to the Thymatron™ System IV ECT instrument that enables the user to acquire, process and display 4 channels of EEG, EMG and ECG data on a PC computer via the rear-panel RS232 serial port. The real-time monitoring feature of the GENIE™ IV also allows the operator to use a PC screen as a 4-channel oscilloscopic monitor during the ECT seizure, while simultaneously storing all data points for later analysis.**

**A *Patient Information* window allows the operator to enter patient identifying data and clinical information using the computer keyboard.**

**The system was designed and engineered to minimize training time and allow "hands on" use almost immediately. It is *Windows 95-98* compliant, enabling the operator to use all the features of the *Windows* environment.**

**A certain amount of redundancy has been built in to the program to make it easier to operate (e.g., playback speed can be adjusted from the CONTROL window, the *Tools* drop-down menu, or by the B key on the computer keyboard)**

## INSTALLATION & SOFTWARE OPERATION

**Connect the Thymatron™ System IV to an IBM™-compatible (desktop or laptop) PC computer, using a 9-pin serial cable: *Connect one end of the cable to the rear-panel serial port (labeled RS232) of the Thymatron™ System IV, and the other end of the cable to a 9-pin serial port on your computer.***

1. **Insert the program diskette in your floppy drive a:**
2. **Create a new folder named "GENIE" on your hard drive (preferably on the *Desktop*) for the Genie™ IV EEG analysis program and your data files.**
3. **Copy the file *Genie IV.exe* from the floppy disk to the new folder you have just created.**
4. **Using the program *Genie IV.exe*, copy the sample patient data file *Sample.dat* into the same folder.**
5. **Open your GENIE™ folder and click on the Genie IV icon to view the menus and utilities, as follows:**

***[NOTE: See under the REPORT section below for instruction on how to create a patient data file in GENIE™ IV by direct transfer of treatment results from the Thymatron™ System IV]***

**Title Bar Headings:**

***File*** **Used to open existing files, set up data for printing, print, and exit.**

***Connect*** **Sends and receives data to and from the Thymatron; sends user's name to Thymatron™ System IV as the heading of the printed treatment report; selects parallel port.**

***PatientInfo*** **Used to enter patient identifying information and comments.**

***Spectrum*** ***Appears only when FFT, BANDS, or SPECTRUM windows are open.*** **Used to select pairs of EEG channels for analysis; to specify whether the analysis will cover the entire EEG or just the current segment; and to assign numerical values to frequency bands.**

***Tools*** ***Appears only when a window is open.*** **Used to open/close the SETTING window for adjusting *scale* and *artifact rejection* settings for all the channels; to set the playback *speed*; and to initiate *playback, reset,* and *reject* functions (these last 3 can also be accessed from the CONTROL window, as described below).**

***Window***

**Used to display a copy of the printed report [when a patient data file is open]; to open/close the CONTROL window for *playback, reset, reject,* and *data collection* functions; to close all windows; and to open and close various display windows, as follows:**

***Graph*:** **Provides real-time monitoring display of EEG, ECG, and EMG tracings. Replays raw EEG, ECG, and EMG as continuous tracings**

***FFT*:** **Displays bar graphs of the frequency composition of the data.**

***Bands*:** **Displays frequency bands of the data.**

***Spectrum:*** **Displays each individual frequency band.**

***"HOT" KEYS*: You can also use accelerator ("hot") keys on the computer keyboard to facilitate data replay. Pressing these keys produces the same effects as clicking on the display.**

**Use the B key to control PlayBack**
**Use the R key to control Reset**
**Use the J key to control Reject**

***FOCUS* feature: A border appears around the most recently-used button to *focus* your attention; use the *Space* bar on the computer keyboard to control whichever button is in Focus.**

**EEG ANALYSIS**

**The Genie™ IV features 5 different display windows: REPORT,GRAPH, BANDS, FFT, and SPECTRUM, as follows.**

***REPORT***

**The report window duplicates the final report as printed on the thermal printer of the Thymatron™ System IV. It will not change with artifacting or time limitation.**

**To open the REPORT window with the demo patient file that accompanies this program, click on:**

**File→Open→Hh6.dat [logo]→Open**

**(If a patient data file is already open, you can also open the REPORT window from *Window* on the title bar.)**

**To open the REPORT window using a patient data file of your own, you must first have stored your patient's data using the *Connect* utility of the GENIE™ IV program in conjunction with the DATA OUT utility of the Thymatron™ System IV, as follows:**

***[NOTE: The following assumes you have administered an ECT treatment with the Thymatron™ System IV properly configured to collect EEG and other physiologic data as described in the Thymatron™ System IV Instruction Manual, and have neither turned off the POWER switch nor unplugged the unit prior to attempting to transfer the treatment results]***

**Make sure your PC is connected to the rear-panel RS232 (serial) port of the Thymatron™ System IV with a 9-pin male to 9-pin female ( modem extension) cable, and that you have opened your GENIE™ folder and clicked on the *Genie IV* program as described above under INSTALLATION & SOFTWARE OPERATION).**

1. **Press the *FlexDial*™; the most recently-set *FlexDial*™ function (e.g., SETTING") will appear on the 8-character L.E.D.**
2. **Rotate the dial left or right until "DATA OUT" is displayed.**
3. **Press the *FlexDial*™; "REPRINT" will flash. Rotate the *FlexDial*™ until "RAW DATA" flashes in the display.**

4. **Click *Connect* in the title bar of the GENIE™ IV program on your PC, then click on *Receive data* in the pull-down menu.**
5. **Press the *FlexDial*™ to initiate data output to the PC. *[NOTE: If no treatment data is stored in memory the message "EMPTY" will flash and no data transfer will occur]***
6. **To EXIT and return to DATA OUT, turn the dial until "EXIT" is flashing and press the dial,**

**or,**

7. **Press the START/STOP button to exit the *FlexDial*™ shell.**

**To close the patient data file close the REPORT window by clicking on X in the upper right-hand corner. [If you made any changes to the data you will be prompted to save the changed file using different file name.]**

***GRAPH***

**This window serves as a 4-channel monitor-analyzer, displaying 2 channels of EEG plus either EMG & ECG, or 2 additional channels of EEG, in 1.28 second epochs. A patient data file (e.g., the *Sample.dat* file on the accompanying diskette) must first be opened as described above in order to display the tracings in the GRAPH window.**

**When you click on *Graph*, the GRAPH window will open, together with the CONTROL and SETTING windows as described below (the CONTROL and SETTING windows can also be opened/closed directly from *Window* and *Tools*, respectively, on the title bar).**

**The GRAPH window can be moved and resized using standard Windows 95 procedures, but the CONTROL and SETTING windows can only be moved, not resized.**

**MONITORING FUNCTION**

**To use your PC screen to monitor up to 4 channels in real time during an ECT treatment, click on:**

***Window→Graph→Monitor***

**Presss the IMPEDANCE TEST button of the Thymatron™ System IV to start transmitting the data to be monitored on the PC screen. Press the START/STOP button to terminate data transmission. The maximum monitoring time for any single treatment is approximately 14 min.**

**To save the treatment data just monitored, download it to your PC using the DATA OUT facility as described above.**

**REVIEW FUNCTION**

**To review a real-time graphic display of the 4-channel recording already collected, click on:**

***Window→Graph→PlayBack* button (in CONTROL window)**

**Select playback speed (100%, 200% or 500% of real time) from the CONTROL window or by clicking on *Speed* in the drop-down menu from *Tools* in the title bar. [The CONTROL window can also be opened/closed by clicking on *Play control* in the drop-down menu from *Window* in the title bar.]**

**If you wish to playback and analyze only *part* of the tracing (e.g., the portion from 10 to 20 sec), select the time using the *time set* feature in the CONTROL window, following the format xx-xx (e.g., 10-20) in seconds. The exact number of seconds elapsed as shown on the CONTROL window timer may differ slightly from your setting because of the 1.28 sec epoch length.**

**You can stop playback any time by clicking on *StopBack* in the CONTROL window.**

**To reject an epoch, click on the CONTROL window *Reject* button (or the J key on the keyboard) during playback of the epoch in question, and the 1.28 second segment will be dropped from the analysis.**

**For each channel, the *scale* (10 to 2000 microvolt) and the automatic *artifact rejection level* (20 to 1000 microvolt) are selected from the SETTINGS window (accessed by clicking *Channels setting* on the pull-down menu from *Tools* in the title bar). A segment will be rejected either automatically when the amplitude exceeds the preset amplitude value selected, or manually when the user clicks the *Reject* button in the CONTROL window.**

**Click on the *Reset* button in the CONTROL window (or the R key on the keyboard) to "rewind" the recording back to the beginning.**

**Select *Connect* from the menu to receive and store patient data from the Thymatron™ System IV, using its DATA OUT utility.**

***FFT***

**This feature provides a continuously updated, real-time, 32 bar, graphic display of the FFT analysis of the EEG in channels 1 & 2 only.**

**Clicking on *Spectrum* in the title bar provides a choice of viewing a static graphic display of either the entire (*Accumulated spectrum*) power spectral analysis, or the analysis for the *Current segment* only.**

**The CONTROL and SETTING windows have the same functions as described earlier.**

***BANDS***

**BANDS provides numeric values for *absolute EEG power*, *relative EEG power*, *% interhemispheric coherence*, and *% interhemispheric asymmetry*, for each of the 4 standard frequency bands (*delta, theta, alpha, beta*), using either preset or user-defined values, plus 2 additional user-assignable bandwidths. These variables are used to assess the relative inter-hemispheric symmetry in EEG *amplitude* and *phase* .**

**NOTE: The user can choose to view a continuously-updated real-time display for these and other variables described below by clicking on *Accumulated Spectrum* in the pull-down menu from *Spectrum* in the title bar, or view the analysis of the current segment only, by clicking on *Current segment* in the pull-down menu.**

**The mean EEG frequency is also displayed for each channel.**

**To change the EEG frequency band limits select from the title bar and pull-down menus as follows:**

**Spectrum→Set bands→[choose band]→click on displayed value→enter new value→click OK**

**You may set up us many BANDS windows as needed by selecting from the title bar and drop-down menu:**

**Window→Bands**

**If 4 EEG channels are being analyzed you may click on *Spectrum* in the title bar to select any combination of 2 of the four channels (e.g., 1&2, 2&4, etc.) to compare against each other by clicking *Spectrum* on the title bar and then selecting the desired channel pair(s) from the pull-down menu:**

**Spectrum→EEG [channel]&[channel]**

**The BANDS window can also be set to display a continuously-updated real-time display, or a display of the current segment only, using the *Accumulated spectrum* and *Current segment* choices in the pull-down menu from *Spectrum* in the title bar.**

***SPECTRUM***

**This window provides a complete array of numeric values for *absolute power, relative power*, *asymmetry*, and *coherence* for each of 32 frequency points, in steps of 0.78 Hz each. *[NOTE: The SPECTRUM window must be opened from the pull-down menu of Window in the title bar—it is not the same as Spectrum in the title bar, which is described above]***

**If 4 EEG channels are being analyzed you may select any combination of 2 of the four channels for analysis, as described above under BANDS.**

**As for BANDS, the SPECTRUM window can also be set to display a continuously-updated real-time display, or a display of the current segment only, using the *Accumulated spectrum* and *Current segment* choices in the pull-down menu from *Spectrum* in the title bar.**

# EXHIBIT 24

Swartz 4-1-21
Exhibit 17

SOMATICS, LLC
Makers of the Thymatron®

The Source to Fill All Your ECT Needs.

Home
Catalog
Downloads
Distributors

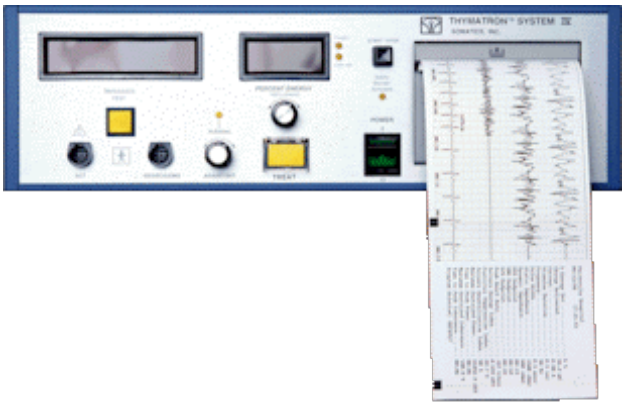
# Thymatron® System IV

view/download/print our brochure



back to Main Catalog

## Specifications



| | |
|---|---|
| Current: | 0.9 A constant, isolated from line current |
| Frequency: | 10 to 70 Hz in 10 Hz increments (to 140 Hz for 0.25 ms pulse) |

| | |
|---|---|
| Pulsewidth: | 0.25 to 1.5 ms in 0.25 ms increments. The Thymatron System IV is available with either 0.25 or 0.30 ms pulsewidth for ultrabrief stimuli, but not both. In North America the customer can specify his choice. In some countries the ultrabrief pulsewidth provided is according to standard practice there. |
| Duration: | 0.14 to 8.0 s in increments of equal charge |
| Maximum: | 504 mC (99.4 J @ 220 ohm); 1008 mC (188.8 J @220 ohm) with double-dose option (where available) |

## Recording

8 user-selectable gain positions for EEG channels (10, 20, 50, 100, 200, 500, and 2000 µV/cm) and EMG/ECG channels (50, 100, 250, 500, 1000, 2500, 5000 and 10,000 µV/cm)

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## Requirements

100-130 volts A.C., 60 Hz, single phase. 100 VA./220-240 volts, 50/60 Hz switchable.

## Approvals

CSA, CE, ISO 13485:2003, TUV, FDA, IEC 60601

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**contact us** | **references**

# EXHIBIT 25

**POOLE & SHAFFERY, LLP**
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SOMATICS, LLC

**UNITED STATES DISTRICT COURT**
**CENTRAL DISTRICT OF CALIFORNIA**

MARCIA BENJAMIN; DANIEL BENJAMIN; JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; individually, and on behalf of all others similarly situated,

Plaintiffs,

vs.

MECTA CORPORATION; SOMATICS, LLC; and DOES 1 through 10, inclusive

Defendants.

Case No.: 2:17-CV-06686-RGK-PJW
[Assigned to Hon. R. Gary Klausner, Court Room 850]

**DEFENDANT SOMATICS, LLC'S RESPONSE TO PLAINTIFFS' REQUEST FOR ADMISSION NO. 30 [SET ONE]**

**PROPOUNDING PARTY:** Plaintiffs, JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; MARCIA BENJAMIN; and DANIEL BENJAMIN

**RESPONDING PARTY:** Defendant, SOMATICS, LLC

**SET NO:** ONE (1)

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COMES NOW, Defendant, SOMATICS, LLC, ("Responding Party"), and pursuant to Rule 36 of the Federal Rules of Civil Procedure, provides its response to Requests for Admission No. 30 (Set 1) propounded by Plaintiffs, JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; MARCIA BENJAMIN; and DANIEL BENJAMIN ("Propounding Party").

**PRELIMINARY STATEMENT**

This response is made solely for the purpose of this action. Each response is subject to all objections as to competence, relevance, materiality, propriety, and admissibility, and any and all other objections and grounds that would require the exclusion of any document or statement contained herein if such document or any statement contained herein were made by a witness present and testifying in court, all of which objections and grounds are reserved and may be interposed at the time of trial.

IT SHOULD BE NOTED that this Responding Party has not fully completed its investigation of the facts relating to the case, has not fully completed discovery in this action, and has not completed preparation for trial. Therefore, the response contained herein is based only on such information and documents as are presently available to and specifically known by Responding Party. It is anticipated further discovery, independent investigation, legal research, and analysis may supply additional facts and documents, add meaning to the known facts as well as establish entirely new factual conclusions and legal conclusions, all of which may lead to substantial additions to, changes in, and variations from the contentions herein set forth. The following response to Propounding Party's discovery requests is given without prejudice to Responding Party's rights to produce evidence of any documents or facts subsequently discovered or recalled. Accordingly, Responding Party reserves the right to change any and all responses herein as additional facts are discovered or ascertained, analyses are made, legal research is completed, and

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contentions are made in a good faith effort to supply as much material and factual information and as much specification of legal contentions as are presently known but should in no way be to the prejudice of the responding party in relation to further discovery, research, and analysis.

**DEFINITIONS**

"PLAINTIFFS", as used throughout these Requests, shall mean Plaintiff JOSE RIERA, MICHELLE RIMES, DIANE SCURRAH, DEBORAH CHASE, MARCIA BENJAMIN, and DANIEL BENJAMIN.

"SOMATICS", as used throughout these Requests, shall mean SOMATICS LLC and any of its officers, directors, employees, agents and representatives and all persons acting or purporting to act on its behalf.

"MECTA", as used throughout these Requests, shall mean MECTA CORPORATION and any of its officers, directors, employees, agents and representatives and all persons acting or purporting to act on its behalf.

"DEFENDANTS", as used throughout these Requests, shall refer to both SOMATICS and MECTA collectively.

"ECT", as used throughout these Requests, shall mean "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." 21 C.F.R. §882.5940(a).

"DOCUMENT" or "DOCUMENTS", as used throughout these Requests, are used in the broadest permissible sense under the Federal Rules of Civil Procedure and shall include, without limitation, tangible things and all written, typewritten, recorded (including audio or videotape or both), graphic, photographic (including negatives), facsimile transmissions, and/or computerized materials in whatever form, including copies, drafts, and

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reproductions thereof to which you have or have had access and every copy of such document which contains any commentary or notation not appearing on the original.

"PERSON", as used throughout these Requests, shall include any natural person, entity or business of any form, and any legal or governmental entity or association.

"TESTING", as used throughout these Requests, shall include any testing or clinical trials conducted according to scientific methodology and protocol.

"SAFETY INFORMATION", as used throughout these Requests, shall mean a summary of and citation to all information known or available about the safety and effectiveness of an ECT device.

"ADVERSE EVENT(S)", as used throughout these Requests, shall mean units of information reasonably suggesting that an ECT device: "(1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and this device or a similar device that [the manufacturer has marketed] would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur." 21 C.F.R. §803.50(a).

"AWARE", as used throughout these Requests, shall mean to "receive or otherwise become aware of information, from any source". 21 C.F.R. §803.50(b).

"REASONABLY KNOWN", as used throughout these Requests, shall mean "(i) [a]ny information that you can obtain by contacting a user facility, importer, or other initial reporter; (ii) any information in your possession; or (iii) any information that you, can obtain by analysis, testing, or other evaluation of the device." 21 C.F.R. §803.50(b).

"SUBSTANTIALLY EQUIVALENT devices, as used throughout

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these Requests, shall mean that devices that are not "different in design and function", specifically, pursuant to 21 C.F.R. §860.30), "do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."

**RESPONSE TO REQUESTS FOR ADMISSION NO. 30**

**REQUEST FOR ADMISSION NO. 30**

Admit, prior to the filing of this lawsuit on September 11, 2017, SOMATICS did not report any ADVERSE EVENTS to the FDA for any SOMATICS ECT device.

**RESPONSE TO REQUEST FOR ADMISSION NO. 30**

Objection. Vague, ambiguous and overbroad as to the term "report." Subject to and without waiving any objection: Admit.

DATED: June 15, 2018

**POOLE & SHAFFERY, LLP**

By: _____
David S. Poole
Jason A. Benkner
Attorneys for Defendant
SOMATICS, LLC

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**VERIFICATION**

UNITED STATES DISTRICT COURT-CENTRAL DISTRICT OF CALIFORNIA

I have read the foregoing **DEFENDANT SOMATICS, LLC'S RESPONSE TO PLAINTIFFS' REQUEST FOR ADMISSION NO. 30 [SET ONE]**

_✓_ CHECK APPLICABLE PARAGRAPH

___ I am a party to this action. The matters stated in the foregoing document are true of my own knowledge.

_✓_ I am __ an officer __ a partner _✓_ an authorized representative, and am authorized to make this verification for that reason.

_____ I am informed and believe and on that ground allege that the matters stated in the foregoing document are true.

___ The matters stated in the foregoing document are true of my own knowledge except as to those matters which are stated on information and belief, and as to those matters I believe them to be true.

___ I am one of the attorneys for _____, a party to this action. Such party is absent from the county aforesaid where such attorneys have their offices, and I make this verification for and on behalf of that party for that reason. I am informed and believe and on that ground allege that the matters stated in the foregoing document are true.

Executed on June 12, 2018 at Vancouver, WA (city, state). I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Conrad Swartz
Print Name

Signature

F:\Clients2\977\1701 - RIERA V. MECTA CORP\DISCOVERY\TO CL\RFA 30-Set1Verif.docx

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**PROOF OF SERVICE**

(F.R.Civ.P. Rule 5(b); U.S.D.C., C.D. Cal., L.R. 5-3; C.C.P. §§ 1013a, 2015.5)

**Jose Riera, et al. v. Mecta Corporation, et al.**
United States District Court Case No. 2:17-CV-06686-RGK-PJW

I am employed in the County of Los Angeles, State of California; I am over the age of 18 years and not a party to the within action; my business address is 400 S. Hope Street, Suite 720, Los Angeles, CA 90071.

On **June 15, 2018**, I served the foregoing document described as: **DEFENDANT SOMATICS, LLC'S RESPONSE TO PLAINTIFFS' REQUEST FOR ADMISSION NO. 30 [SET ONE]** on the interested parties in said action in a sealed envelope addressed as follows:

SEE ATTACHED SERVICE LIST

☐ By Mail [Federal] I placed such envelope with postage thereon fully prepaid in the United States mail at Los Angeles, California.

☒ (BY COURT'S CM/ECF SYSTEM) Pursuant to Local Rule, I electronically filed the documents with the Clerk of the Court using the CM/ECF system, which sent notification of that filing to the persons listed below

☐ I caused said document(s) to be transmitted by email to each addressee set forth below on this date. The transmission of this document was complete and without error.

☐ I caused such envelope to delivered via overnight delivery to the party(ies) listed on the attached mailing list.

Executed on **June 15, 2018**, at Los Angeles, California.

☐ [State] I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

☒ [Federal] I declare that I am employed in the office of a member of the bar of this Court at whose direction this service was made.

/S/ Nicole Lyons
Nicole Lyons, Declarant

**SERVICE LIST**

**Jose Riera, et al. v. Mecta Corporation, et al.**
United States District Court Case No. 2:17-CV-06686-RGK-PJW

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**UNITED STATES DISTRICT COURT**
**CENTRAL DISTRICT OF CALIFORNIA**

MARCIA BENJAMIN; DANIEL BENJAMIN; JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; individually, and on behalf of all others similarly situated,

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vs.

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Case No.: 2:17-CV-06686-RGK-PJW
[Assigned to Hon. R. Gary Klausner, Court Room 850]

**DEFENDANT SOMATICS, LLC'S RESPONSE TO PLAINTIFFS' REQUESTS FOR ADMISSION [SET ONE]**

**PROPOUNDING PARTY:** Plaintiffs, JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; MARCIA BENJAMIN; and DANIEL BENJAMIN

**RESPONDING PARTY:** Defendant, SOMATICS, LLC

**SET NO:** ONE (1)

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COMES NOW, Defendant, SOMATICS, LLC, ("Responding Party"), and pursuant to Rule 36 of the Federal Rules of Civil Procedure, provides its responses to Requests for Admission (Set 1) propounded by Plaintiffs, JOSE RIERA; MICHELLE HIMES; DIANE SCURRAH; DEBORAH CHASE; MARCIA BENJAMIN; and DANIEL BENJAMIN ("Propounding Party").

**PRELIMINARY STATEMENT**

These responses are made solely for the purpose of this action. Each response is subject to all objections as to competence, relevance, materiality, propriety, and admissibility, and any and all other objections and grounds that would require the exclusion of any document or statement contained herein if such document or any statement contained herein were made by a witness present and testifying in court, all of which objections and grounds are reserved and may be interposed at the time of trial.

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contentions are made in a good faith effort to supply as much material and factual information and as much specification of legal contentions as are presently known but should in no way be to the prejudice of the responding party in relation to further discovery, research, and analysis.

**DEFINITIONS**

"PLAINTIFFS", as used throughout these Requests, shall mean Plaintiff JOSE RIERA, MICHELLE RIMES, DIANE SCURRAH, DEBORAH CHASE, MARCIA BENJAMIN, and DANIEL BENJAMIN.

"SOMATICS", as used throughout these Requests, shall mean SOMATICS LLC and any of its officers, directors, employees, agents and representatives and all persons acting or purporting to act on its behalf.

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reproductions thereof to which you have or have had access and every copy of such document which contains any commentary or notation not appearing on the original.

"PERSON", as used throughout these Requests, shall include any natural person, entity or business of any form, and any legal or governmental entity or association.

"TESTING", as used throughout these Requests, shall include any testing or clinical trials conducted according to scientific methodology and protocol.

"SAFETY INFORMATION", as used throughout these Requests, shall mean a summary of and citation to all information known or available about the safety and effectiveness of an ECT device.

"ADVERSE EVENT(S)", as used throughout these Requests, shall mean units of information reasonably suggesting that an ECT device: "(1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and this device or a similar device that [the manufacturer has marketed] would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur." 21 C.F.R. §803.50(a).

"AWARE", as used throughout these Requests, shall mean to "receive or otherwise become aware of information, from any source". 21 C.F.R. §803.50(b).

"REASONABLY KNOWN", as used throughout these Requests, shall mean "(i) [a]ny information that you can obtain by contacting a user facility, importer, or other initial reporter; (ii) any information in your possession; or (iii) any information that you, can obtain by analysis, testing, or other evaluation of the device." 21 C.F.R. §803.50(b).

"SUBSTANTIALLY EQUIVALENT devices, as used throughout

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these Requests, shall mean that devices that are not "different in design and function", specifically, pursuant to 21 C.F.R. §860.30), "do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."

**RESPONSES TO REQUESTS FOR ADMISSION**

**REQUEST FOR ADMISSION NO. 1**

Admit SOMATICS is currently a manufacturer of ECT devices.

**RESPONSE TO REQUEST FOR ADMISSION NO. 1**

Admit

**REQUEST FOR ADMISSION NO. 2**

Admit that, from at least September 4, 1979 through to the present, SOMATICS has caused ECT devices manufactured by SOMATICS to be distributed for use within the United States.

**RESPONSE TO REQUEST FOR ADMISSION NO. 2**

Deny

**REQUEST FOR ADMISSION NO. 3**

Admit that SOMATICS knows of no manufacturer of ECT devices for distribution within the United States since January 1, 1985, other than the two DEFENDANTS.

**RESPONSE TO REQUEST FOR ADMISSION NO. 3**

Deny

**REQUEST FOR ADMISSION NO. 4**

Admit that an ECT device, pursuant to 21 Code of Federal Regulation §882.5940(a), is "a device used for treating severe psychiatric

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**RESPONSE TO REQUEST FOR ADMISSION NO. 33**

Deny

**REQUEST FOR ADMISSION NO. 34**

Admit SOMATICS did not investigate any of the PLAINTIFFS' allegations of brain injury within 30 days of the service of the Complaint in this lawsuit.

**RESPONSE TO REQUEST FOR ADMISSION NO. 34**

Admit

**REQUEST FOR ADMISSION NO. 35**

Admit SOMATICS did not make an ADVERSE EVENT report to the FDA as to any of the PLAINTIFFS within 30 days of the service of the Complaint in this lawsuit.

**RESPONSE TO REQUEST FOR ADMISSION NO. 35**

Admit

**REQUEST FOR ADMISSION NO. 36**

Admit that in 2009 the FDA opened a public docket (the "DOCKET") for comments relative to the potential reclassification of ECT devices (74 Fed. Reg. 46607).

**RESPONSE TO REQUEST FOR ADMISSION NO. 36**

Admit

**REQUEST FOR ADMISSION NO. 37**

Admit that there were hundreds of comments submitted to the DOCKET, reflected in 80 Fed.Reg. at 81226, of ECT patients reporting permanent memory loss following treatment.

**RESPONSE TO REQUEST FOR ADMISSION NO. 37**

Responding Party lacks sufficient information and belief to admit or deny this request.

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**REQUEST FOR ADMISSION NO. 38**

Admit that there were hundreds of comments submitted to the DOCKET, reflected in 80 Fed.Reg. at 81226, of ECT patients reporting brain damage following treatment.

**RESPONSE TO REQUEST FOR ADMISSION NO. 38**

Responding Party lacks sufficient information and belief to admit or deny this request.

**REQUEST FOR ADMISSION NO. 39**

Admit that patients who had received ECT treatment from SOMATICS ECT devices submitted ADVERSE EVENTS to the DOCKET.

**RESPONSE TO REQUEST FOR ADMISSION NO. 39**

Responding Party lacks sufficient information and belief to admit or deny this request.

**REQUEST FOR ADMISSION NO. 40**

Admit that in 2009 SOMATICS was AWARE of the DOCKET.

**RESPONSE TO REQUEST FOR ADMISSION NO. 40**

Admit

**REQUEST FOR ADMISSION NO. 41**

Admit that no later than December 31, 2010, SOMATICS had reviewed the comments submitted to the DOCKET.

**RESPONSE TO REQUEST FOR ADMISSION NO. 41**

Admit

**REQUEST FOR ADMISSION NO. 42**

Admit SOMATICS did not investigate any of the ADVERSE EVENTS submitted to the DOCKET.

**RESPONSE TO REQUEST FOR ADMISSION NO. 42**

Admit

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**RESPONSE TO REQUEST FOR ADMISSION NO. 65**

Objection. This request seeks admission of a fact which is no longer relevant to this action.

**REQUEST FOR ADMISSION NO. 66**

Admit that a SOMATICS ECT device was used to administer ECT treatment to Plaintiff Diane Scurrah.

**RESPONSE TO REQUEST FOR ADMISSION NO. 66**

Objection. This request seeks admission of a fact which is no longer relevant to this action.

**REQUEST FOR ADMISSION NO. 67**

Admit that a SOMATICS ECT device was used to administer ECT treatment to Plaintiff Deborah Chase.

**RESPONSE TO REQUEST FOR ADMISSION NO. 67**

Responding Party lacks sufficient information and belief and is therefore unable to admit or deny.

**REQUEST FOR ADMISSION NO. 68**

Admit that a SOMATICS ECT devise was used to administer ECT treatment to Plaintiff Marcia Benjamin.

**RESPONSE TO REQUEST FOR ADMISSION NO. 68**

Objection. This request seeks admission of a fact which is no longer relevant to this action.

DATED: July 2, 2018

**POOLE & SHAFFERY, LLP**

By: _____
David S. Poole
Jason A. Benkner
Attorneys for Defendant
SOMATICS, LLC

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VERIFICATIONS TO FOLLOW

**PROOF OF SERVICE**

(F.R.Civ.P. Rule 5(b); U.S.D.C., C.D. Cal., L.R. 5-3; C.C.P. §§ 1013a, 2015.5)

**Jose Riera, et al. v. Mecta Corporation, et al.**
United States District Court Case No. 2:17-CV-06686-RGK-PJW

I am employed in the County of Los Angeles, State of California; I am over the age of 18 years and not a party to the within action; my business address is 400 S. Hope Street, Suite 720, Los Angeles, CA 90071.

On July 2, 2018, I served the foregoing document described as: **DEFENDANT SOMATICS, LLC'S RESPONSE TO PLAINTIFFS' REQUESTS FOR ADMISSION [SET ONE]** on the interested parties in said action in a sealed envelope addressed as follows:

SEE ATTACHED SERVICE LIST

☒ By Mail [Federal] I placed such envelope with postage thereon fully prepaid in the United States mail at Los Angeles, California.

☐ (BY COURT'S CM/ECF SYSTEM) Pursuant to Local Rule, I electronically filed the documents with the Clerk of the Court using the CM/ECF system, which sent notification of that filing to the persons listed below

☐ I caused said document(s) to be transmitted by email to each addressee set forth below on this date. The transmission of this document was complete and without error.

☐ I caused such envelope to delivered via overnight delivery to the party(ies) listed on the attached mailing list.

Executed on July 2, 2018, at Los Angeles, California.

☐ [State] I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

☒ [Federal] I declare that I am employed in the office of a member of the bar of this Court at whose direction this service was made.

Nicole Lyons, Declarant

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## SERVICE LIST

**Jose Riera, et al. v. Mecta Corporation, et al.**
United States District Court Case No. 2:17-CV-06686-RGK-PJW

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Attorneys for Plaintiffs,
Jose Riera, Michelle Himes, Diane Scurrah, Deborah Chase, individually, and on behalf of all others similarly situated

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# EXHIBIT 26

**REGULATORY UPDATE TO THYMATRON® SYSTEM IV INSTRUCTION MANUAL**

Caution: Federal law restricts this device to sale by or on the order of a licensed physician.

ECT is a complex medical procedure. Its proper and safe conduct requires a staff of licensed healthcare professionals who are trained and experienced with the associated procedures, have received clinical privileges for ECT from the appropriate hospital committee, and have carefully read and are thoroughly familiar with the medical literature concerning the risks, benefits, complications, and methods of ECT. This literature includes the major textbooks of ECT, publications about ECT that have appeared in the major journals of psychiatry, the Journal of ECT, and the American Psychiatric Association's The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging – A Task Force Report (2001) . As with other aspects of medical practice, knowledge about ECT continues to change, and clinicians are responsible for maintaining awareness of these changes from these publications and other sources.

It is essential that doctors planning to use the Thymatron® System IV read and follow the warnings and recommendations of the Task Force Report of the American Psychiatric Association as set forth in "The Practice of Electroconvulsive Therapy" (APA, 2001), which states, in part, that "A small minority of patients treated with ECT later report devastating cognitive consequences. Patients may indicate that they have dense amnesia extending far back into the past for events of personal significance or that broad asof cognitive function are so impaired that the patients are no longer able to engage in former occupations...in some patient self-reports of profound ECT-induced deficits may reflect objective loss of function...In rare cases, ECT may result in a dense and persistent retrograde amnesia extending to years..."

INDICATIONS FOR USE

The U.S. Food and Drug Administration has indicated ECT for use in the treatment of severe major depressive episodes associated with major depressive disorder (MDD) or bipolar depressive disorder (BPD) in patients 18 years of age and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition.

The Thymatron® System IV is intended to be used to administer electroconvulsive therapy (ECT) to patients suffering from mental disorders in which a rapid, definitive response is desired. ECT is most often indicated in patients who have not responded to adequate courses of appropriate pharmacotherapies but is also indicated as the primary treatment for patients in whom a rapid or high probability of response is desired (as when they are severely medically ill or in danger of harming themselves) or who are known by their treatment history to respond only to ECT, or who have expressed a valid preference for ECT over alternate therapies.

SAFETY INFORMATION

Please read the following important safety requirements before using the Thymatron® System IV ECT Instrument.

WARNINGS

WARNING: Do not remove the top or bottom covers of the Thymatron® System IV. There are no user serviceable parts inside. Any servicing must be performed by qualified service personnel.



**REGULATORY UPDATE TO THYMATRON® SYSTEM IV INSTRUCTION MANUAL**

WARNING: Do not use any cables or lead wires that appear to be damaged.

WARNING: The Thymatron® System IV is defibrillator protected.
Nevertheless, for safety reasons, all cable connections between the Thymatron® System IV ECT Instrument and the patient must be disconnected prior to initiation of the defibrillation stimulus.

WARNING: Avoid the risk of accidental shock to medical personnel. Do not contact the patient, or any conductive surface touching the patient, unless wearing electrically insulated gloves. If holding the patient's jaw or touching the patient's head during the electrical stimulus, make sure to use electrically insulating gloves.

WARNING: Administering ECT to a patient with an implanted DBS device can damage the DBS device or cause it to malfunction and cause injury to the patient.

WARNING: Specific patient conditions may be associated with substantially increased risk from ECT. These include unstable or severe cardiovascular conditions (recent myocardial infarction, unstable angina, poorly-compensated
congestive heart failure, severe valvular cardiac disease), vascular aneurysms susceptible to rupture with increased blood pressure, increased intracranial pressure, recent cerebral infarction, severe chronic obstructive pulmonary disease, asthma, pneumonia and anesthesia risk level ASA 4 or 5.

PRECAUTIONS

CAUTION: Do not subject the Thymatron® System IV to extreme moisture, and do not use it after it has been partially or totally immersed in liquid or when a significant amount of liquid has been spilled on it. Power the unit off and have it checked by a qualified technician before powering it on or using it again.

CAUTION: Only use the Thymatron® System IV with the Somatics' Treatment or Monitoring Cables.

CAUTION: The Treatment and Monitoring Cables are not interchangeable and cannot be inserted into the wrong front panel connector. Attempting to force the Treatment Cable into the connector intended for the Monitoring Cable (and vice versa) will damage both the connector and the cable.

CAUTION: The ECG function of the Thymatron System IV is used only to obtain a heartrate to help assess the efficacy of the seizure; it is not intended to be used to make diagnoses. Do not use the Thymatron System IV ECG function to monitor the patient's heart for any other purpose.

CAUTION: The EMG function of the Thymatron System IV is used only to obtain an estimate of the motor seizure duration to help assess the efficacy of the seizure; it is not intended to be used to make diagnoses. Do not use the Thymatron System IV EMG function to monitor the patient's nerve activity for any other purpose.

CAUTION: Do not dispose of your Thymatron® System IV in the general waste. As per Directive 2002/96/EC for the disposal of electrical and electronic equipment, please contact the manufacturer for instructions.

**REGULATORY UPDATE TO THYMATRON® SYSTEM IV INSTRUCTION MANUAL**

CAUTION: Prior to initiating ECT on a patient with a cochlear implant, healthcare professionals should discuss the issue with an otolaryngologist or audiologist and review the cochlear implant Instructions for Use.

CAUTION: Thymapad® electrodes are single-use only and must be discarded after the treatment. The Thymatron® System IV Treatment Cable, Monitoring Cable and lead wires can be cleaned by wiping them off with a Germicidal Disposable Cloth. Steel stimulus electrodes may be cleaned with soapy water or alcohol. The Thymatron® has no special requirements for restricted environment during transport or storage, beyond Standard Sub-clause 10.1 criteria.

ADVERSE EVENTS

Like any therapy, ECT has risks. Certain patients will experience adverse events in conjunction with electroconvulsive therapy. Patients should be made aware of these risks and confirm that they fully understand them prior to consenting to therapy.

The most common reported adverse effects of ECT are:

- Headache.
- Muscle soreness; Mild to moderate pain/discomfort, including jaw pain.
- Nausea.
- Disorientation immediately after seizure induction.
- Memory dysfunction (see further discussion below).

Recent estimates in the medical literature of the mortality rate associated with ECT treatment are 1 per 10,000 patients or 1 per 80,000 treatments.
Other serious adverse events have occurred, including adverse reaction to anesthetic agents / neuromuscular blocking agents; adverse skin reactions (e.g., skin burns); cardiac complications, including arrhythmia, ischemia/infarction (i.e., heart attack), acute hypertension, hypotension, and stroke; cognition and memory impairment; brain damage; dental/oral trauma; general motor dysfunction; physical trauma (i.e., if inadequate supportive drug treatment is provided to mitigate unconscious violent movements during convulsions); hypomanic or manic symptoms (e.g., treatment-emergent mania, postictal delirium or excitement); neurological symptoms (e.g., paresthesia, dyskinesias); tardive seizures; prolonged seizures; non-convulsive status epilepticus; pulmonary complications (e.g., aspiration/inhalation of foreign material, pneumonia, hypoxia, respiratory obstruction such as laryngospasm, pulmonary embolism, prolonged apnea); visual disturbance; auditory complications; onset/exacerbation of psychiatric symptoms; partial relief of depressive anergia enabling suicidal behavior; homicidality; substance abuse; coma; falls; and device malfunction (creating potential risks such as excessive dose administration).

Certain patients are more likely to experience severe adverse events, including those with pre-existing cardiac illness, compromised pulmonary status, a history of brain injury, or medical complications after earlier courses of anesthesia or ECT. Concurrent administration of antipsychotic (neuroleptic) medication may increase the risks of adverse cardiac, pulmonary, and neurological events, and falls. Concurrent administration of stimulants may increase the risks of cardiac and neurological complications, such as prolonged seizure. All of this information should be assessed in developing the treatment plan for a particular patient.

Cognitive side effects are experienced in varying types and severity by ECT patients. Studies have shown that the methods used in ECT administration have a significant impact on the nature and magnitude of cognitive deficits. In general, the American Psychiatric Association recognizes that the following treatment parameters are each independently associated with more intense cognitive side effects:

- Bilateral electrode placement;
- Sine wave stimulation;
- High electrical dosage relative to seizure threshold;
- Closely spaced treatments;
- Larger numbers of treatments;
- Concomitant psychotropic medications;
- High dosage of barbiturate anesthetic agents.

ECT may result in anterograde or retrograde amnesia. Such post-treatment amnesia typically dissipates over time; however, incomplete recovery is possible. In rare cases, patients may experience permanent memory loss or permanent brain damage.

ECT—and use of the Thymatron® System IV specifically—has been shown to be effective in treating major depressive episodes associated with major depressive disorder (MDD) or bipolar depressive disorder (BPD) in patients 18 years of age and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. A few studies performed with the device are highlighted below, with additional references provided in the bibliography.

TECHNIQUE OF ECT

Users of Thymatron ECT devices should carefully follow the specific ECT treatment techniques and procedures outlined in Chapters 6-11 of the American Psychiatric Association's The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging – A Task Force Report (2001)

EFFICACY, SAFETY, AND SIDE-EFFECTS

EFFICACY

A randomized, double-blind, controlled trial of ECT in 230 patients with major depression treated with a Thymatron found 3 different electrode placements equally and significantly effective in reducing depression scale scores, with the greatest effect achieved with traditional bitemporal ECT (Kellner et al, 2010).

A randomized, controlled trial of ECT in 489 major depressive patients, with or without atypical features, treated with a Thymatron DGx. Both the atypical and the typical groups experienced significant improvement in depression (Husain et al, 2008).

A randomized, controlled trial of ECT in 253 unipolar depressed patients with and without psychosis treated with a Thymatron. An 87% overall remission rate was obtained that was greater and more complete in the psychotic depressives (Petrides et al, 2001).

**REGULATORY UPDATE TO THYMATRON® SYSTEM IV INSTRUCTION MANUAL**

SAFETY

Somatics' safety experience with the Thymatron ECT device since 1984 when FDA approved the Somatics Thymatron ECT device for marketing shows that more than 4,300 Thymatron devices have been sold worldwide. During that time Somatics has maintained complete safety files on the Thymatron device, including those required by the FDA's Good Manufacturing Practice regulation, the Canadian Standards Association, and international testing agencies for the CE mark. In the ensuing 34 years there has been no occurrence of a reportable adverse event (death or serious injury) related to the use of a Thymatron ECT device, no reported occurrence of catastrophic ECT component failure, and no product recall issued.

SIDE-EFFECTS

Numerous studies have been conducted to assess the potential adverse events of ECT on cognition and brain structure. The following is a sample of the many that were conducted with the Thymatron device.

14 patients undergoing bilateral ECT were assessed for cognitive performance by psychometric testing on day before ECT and after the 3rd, 6th, and last ECT treatments. Pre-ECT and post- ECT concentrations of neuron-specific enolase (NSE) and protein S-100, two indicators of brain tissue damage, were not significantly different and the authors concluded that modern ECT does not induce brain tissue damage detectable by changes in NSE or S-100 protein (Agelink et al, 2001).

A Thymatron was used to treat 83 unipolar depressives who had been evaluated at baseline on tests of behavioral and semantic memory. One year after a course of bilateral or unilateral ECT neither behavioral memory nor semantic memory scores were reduced from baseline—in fact, bilateral ECT was associated with significantly improved semantic memory (Schat et al, 2007).

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

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JECT 23:153-157

Ende et al (2000)
The Hippocampus in Patients Treated With Electroconvulsive Therapy
Arch Gen Psychiatry 57:937-943

DISCLAIMER / WARRANTIES

Please note that nothing in this manual constitutes, or should be construed as, a claim by Somatics LLC that confusion, cognitive impairment, or memory loss (short-term, long- term, recent, remote, transient, or persistent), or structural brain change (brain damage) cannot occur as the result of ECT or the general anesthesia administered with ECT.

Many patients experience temporary loss of recent or remote memories with ECT, particularly with traditional bilateral ECT. A few patients have reported experiencing persisting loss of memories or memory functions after ECT. Mental and physical illnesses, anesthesia, medications, and postponement of treatment each have their own adverse effects, which can be substantial.

The outcome of ECT treatment depends on many clinical aspects outside the ECT device, including the physical, psychiatric and emotional condition of the patient prior to and at ECT, details of the ECT treatment other than the ECT device settings, including anesthesia and medication exposure. By using the Thymatron System IV, the user accepts responsibility for describing details of those and of pre-existing conditions including brain injury and atrophy, and cognitive difficulties, and for disclosing all appropriate information about risks of ECT to patients, their families and their guardians (if any).

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# EXHIBIT 27

# Addendum for Thymatron System IV Manual

ECT requires a staff of licensed, trained and experienced professionals thoroughly familiar with current literature concerning risks, complications and methods. This literature includes ECT textbooks, journal publications, and the latest American Psychiatric Association ECT Task Force Report. Techniques in Chapters 6-11 of the 2001 edition should be followed. This Task Force Report states: "A small minority of patients treated with ECT later report devastating cognitive consequences. Patients may indicate that they have dense amnesia extending far back into the past for events of personal significance or that broad areas of cognitive function are so impaired that the patients are no longer able to engage in former occupations...self-reports of profound ECT-induced deficits may reflect objective loss of function...In rare cases, ECT may result in a dense and persistent retrograde amnesia extending to years before the treatment..."

ADVERSE EVENTS may occur and patients and their families must be informed of the risks and confirm their understanding in writing. Most common are headache, muscle soreness, jaw pain, other mild to moderate discomfort, nausea, disorientation, and memory dysfunction. Other possibilities include arrhythmia, cardiac complications including ischemia, infarction, hypertension, hypotension; stroke; cognition and memory impairment; dental/oral injury; motor dysfunction; physical injury (if movements are not adequately limited); mania; delirium; agitation; neurological symptoms (e.g., paresthesias, dyskinesias); tardive seizures; prolonged seizures; non-convulsive status epilepticus; pulmonary complications (e.g., aspiration, pneumonia, hypoxia, laryngospasm, pulmonary embolism, prolonged apnea); visual disturbance; hearing disturbance; onset or exacerbation of psychiatric symptoms including depression or anxiety; disinhibition; suicidality; homicidality; substance abuse; coma; falls; skin burns and abrasions; and excessive effect or allergic reactions from anesthetic medication. Device malfunction is possible, with excessive electrical dose and higher risks of adverse events listed above. Death is reported as 1 per 10,000 patients and 1 per 80,000 treatments.

Adverse cognitive effects occur in varying types and severity, and can be higher with bilateral ECT, high electrical dosage, closely spaced treatments, more treatments, concurrent medications, and high anesthetic doses. ECT may produce anterograde amnesia or retrograde amnesia for recent or remote memory. Memory disturbance typically dissipates over time. Claims of permanent memory loss or brain injury have not been substantiated by scientific studies. It can sometimes be impossible to identify specific causes of memory or other cognitive disturbance in patients who receive ECT. No claim is made that any form of ECT, or the anesthesia given with ECT, is incapable of inducing confusion, cognitive impairment, or memory loss.

WARNING: Some conditions incur markedly increased risk from ECT, e.g., cardiac illness, unstable cardiovascular function, aneurysm, cerebral hypertension, recent stroke, severe COPD or other lung impairment, pneumonia, brain injury, complications with previous anesthesia or ECT, anesthesia risk level ASA 4 or 5. Concurrent antipsychotic medication increases risks of adverse cardiac, pulmonary, and neurological

events, including falls and pneumonia. Concurrent stimulant medication increases cardiac and neurological risks, e.g., prolonged seizure, confusion, amnesia.

ECT outcome depends on many factors outside the ECT device, e.g., physical, psychiatric and emotional condition of the patient before ECT, ECT treatment details, medication exposure. By using a Thymatron device the user accepts responsibility for documenting those and pre-existing conditions including brain injury, brain atrophy, and cognitive difficulties. Somatics LLC warrants that reasonable care was used in the design and manufacture of this device. Handling, storage, maintenance and preparation of this device as well as patient related factors such as diagnosis, medical conditions, and medications and other matters beyond the influence of Somatics LLC, influence the results of treatment using this device. Somatics, LLC disclaims responsibility for matters beyond its influence and for any medical complications directly or indirectly resulting from use of this product.

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# EXHIBIT 28

# ELECTROCONVULSIVE THERAPY

Fourth Edition

Richard Abrams, M.D.

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*For Trudy, again and always*

In view of the multiform phenomenon of ECS-induced neurogenesis reported in rodents, which is associated with reversal of atrophy of stress-vulnerable neurons, protection from further damage, and increased neuronal synaptic strength, survival, and growth (Duman and Vaidya, 1998), similar neuronal effects might occur in depressed patients who receive ECT, many of whom already exhibit MRI signs and cognitive symptoms of hippocampal atrophy (Sheline et al., 1999). Were this, in fact, the case, improved memory function after ECT would not be unexpected. It is even conceivable that ECT might exert beneficial effects on memory function in certain neurodegenerative conditions (e.g., Alzheimer's, and Parkinson's diseases). The reliably beneficial effects of ECT in Parkinson's disease, described in detail in Chapter 2, have always been attributed to either an increased availability of dopamine at postsynaptic receptor sites, or an increased sensitivity of those receptors. Might ECT-induced neogenesis of dopamine-containing cells in the substantia nigra constitute the real basis of the observed clinical improvement?

## Prediction of Post-ECT Cognitive Impairment

Scant attention has been paid in the literature to predictors of ECT-induced cognitive impairment other than age, treatment electrode placement, seizure duration, and stimulus dose. In the first study of whether preexisting cognitive impairment constitutes a risk factor, Sobin et al. (1995) examined a sample of 71 depressed patients randomly assigned to high- or low-dose right unilateral or bitemporal ECT, and found that pretreatment global cognitive status assessed via Mini-Mental State Examination (Folstein, Folstein, and McHugh, 1975), and postictal orientation recovery time, were both significantly associated with retrograde amnesia for autobiographical memories 1 week and 2 months after their treatment course, regardless of treatment group assignment. These findings suggest that the Mini-Mental State Examination might be used as a screening test to guide the selection of ECT treatment parameters demonstrated to affect cognition (treatment electrode placement, stimulus characteristics, and frequency of administration), and that postictal disorientation should be routinely assessed for the same purpose.

## Management of Memory Impairment

No specific treatment is available to reduce the extent or duration of the memory impairment of ECT, which occurs in its most pronounced form after bitemporal ECT, especially when administered at a higher dosage levels. The hope generated by early case reports (Weingartner et al., 1981; Partap, Jos, and Dye, 1983) that vasopressin might attenuate ECT-induced memory impairment proved ephemeral in a controlled trial (Mattes et al., 1990).



The physician is thus left with several practical measures to take in the event that emergent confusion and memory loss become problematic during a course of ECT. If sine-wave or conventional bitemporal ECT are being used, the obvious step is to switch to a brief-pulse stimulus and unilateral or bifrontal electrode placement. If a thrice-weekly treatment schedule is in force, reducing the frequency to twice a week will help substantially. The physiological principles discussed in Chapter 6 governing neuronal discharge and recovery should also be applied here, because increasing the efficiency of the stimulus parameter package should reduce cognitive side effects as well as augment the therapeutic impact. Lowering the pulse width to the 0.25 msec to 0.5 msec range, and increasing stimulus duration to 6–8 seconds without altering the dosage, should reduce memory loss and confusion by reducing the charge rate. If bitemporal ECT is being used, the dosage can be reduced to the lowest level that is compatible with inducing a well-developed EEG seizure pattern. However, I recommend against lowering the dosage with unilateral ECT for reasons already specified in Chapters 6 and 7. Fortunately, dosage effects of unilateral ECT on memory and cognition are reported to be undetectable 2 weeks after concluding a treatment course (Sackeim et al., 1993).

## Does ECT Cause Persistent or Permanent Memory Impairment?

Aside from the presentation by Weiner et al. (1986b), which suffers from the problems already discussed, the articles reviewed above include every published study that sought evidence for long-term or persistent memory and nonmemory cognitive effects of brief-pulse ECT. None of these studies demonstrate that any form of brief-pulse ECT, regardless of dosage, is capable of inducing memory deficits even as early as 2 weeks following a course of treatment, much less months later. The fact that significant differences can be found 2 months posttreatment between the amnestic effects of brief-pulse bitemporal and brief-pulse unilateral ECT (Lisanby et al., 2000; Sackeim et al., 2000) in no way demonstrates that persistent adverse effects relative to baseline performance were caused by either method alone; no such information in fact exists. (For example, both methods could cause memory improvement that is simply greater with unilateral placement, a phenomenon that, as noted above, does in fact occur for some measures.)

Moreover, in a unique follow-up study of patients who had received unusually large numbers of ECTs, Devanand et al. (1991) compared 8 patients who had each received more than 100 lifetime treatments with sine-wave, bitemporal ECT (mean of 12 courses and 160 ECTs per patient) with a closely matched control group of depressives who had never received ECT. The 2 groups did not differ on any of the many measures examined of objective or subjective memory functioning.

How then to account for the assertions in a recent editorial that, following ECT, "virtually all patients experience some degree of persistent and, likely, permanent retrograde amnesia." (Sackeim, 2000)? The editorial contains additional statements to the effect that "in many patients the recovery from retrograde amnesia will be incomplete, and there is evidence that ECT can result in persistent or permanent memory loss," "some patients may experience persistent amnesia extending several years prior to ECT," and, most strikingly, "increasing evidence has accumulated that some degree of persistent memory loss [with ECT] is common" (Sackeim, 2000). Notably, none of these statements is supported by literature citation.

The last of these comments suggests that the editorial is not referring primarily to sine-wave therapy because the phrase "increasing evidence has accumulated" can hardly refer to a method that was essentially abandoned more than 20 years ago. Assuming the claims apply at least equally to brief-pulse therapy, what supporting evidence is provided to back them up? Unfortunately, none—the reader is required to accept the statements on faith alone.

It is notable that this editorial introduced a special issue of *Journal of ECT* ("Cognition and ECT") in which there also appears a memoir by a recipient of ECT, entitled "Electroconvulsive Therapy and Memory Loss: A Personal Journey" (Donahue, 2000). The author of the memoir is no overt enemy of ECT—indeed, she states both that ECT may have saved her life, and that had she the decision to make over again, her choice would still be ECT. Moreover, she is highly educated, writes cogently and well, has a thorough knowledge of the relevant literature, and engages in no polemics. Nevertheless, her conviction that she suffered "devastating and permanent memory loss with ECT" is just that: a personal conviction, and one that is, like many other personal convictions, unsupported by any objective evidence.

Because the memoir was solicited for the special cognitive issue of the journal it did not undergo the usual peer-review process; therefore the validity of the assertions it contains is both unknown and unknowable. The sincerity of its author is not in question; the difficulty lies elsewhere, in the disjunction between objective science and subjective experience. No amount of memory or cognitive testing can ever prove or disprove the truth of subjective experience, which is, by definition, inaccessible to the scientific method. (Subjective experience can, of course, be described, classified, catalogued, and the results of that cataloguing analyzed, as in the many useful studies of subjective memory described earlier in this chapter.)

In the absence of any published articles cited in support of the editorial's assertion that virtually all patients receiving ECT likely experience a degree of permanent retrograde amnesia, one might reasonably inquire whether the inclusion of a personal memoir in the special cognitive issue of *Journal of ECT* was intended to substitute for the missing facts. This, of course, it can not do.

Moreover, although as documented above, the overwhelming majority of patients who have received brief-pulse ECT at any dose consider their memory function to be very substantially improved, and although a recent article strikingly reports that patients who receive the most intense form of



titrated brief-pulse ECT (2.5× threshold bitemporal ECT) rate their memory 71% better after ECT than ever before in their life (Sackeim et al., 2000), these self-assessments are discounted as "unlikely" and "of doubtful validity" (Sackeim, 2000). At the same time, however, the editorial unquestioningly accepts as accurate the self-assessments of other patients who "report that a large segment of their life is lost (after having received ECT)." Neither the source of these self-assessments, nor an estimate of their validity, is presented in the editorial, leaving the reader in the dark as to how they should be evaluated.

One problem that has bedeviled all objective follow-up studies of the memory effects of ECT is the fact that comparisons have so far only been made with the patient's cognitive status at pre-ECT baseline—which is to say, while they were depressed—or with normal or depressed no-ECT control groups. Because whatever cerebral process causes melancholia also impairs memory performance (which impairment, in its severest form, presents as the dementia syndrome of depression), memory is invariably impaired immediately prior to ECT, and often for weeks or months earlier. Comparing post-ECT memory performance with immediate pre-ECT performance is therefore problematic: the comparison variable of greatest interest, pre-illness cognitive performance, is unavailable for comparison (hence the instructions of the subjective memory questionnaire that require the patient to compare his present level with the best he has ever before experienced).

Test results obtained from normal individuals can control for this lack to a certain degree, but melancholic patients may never have been entirely normal—their brain function may have been different from the outset, just as the occurrence of Alzheimer's dementia can be predicted from the written compositions of individuals six decades prior to the onset of cognitive symptoms (Snowdon, Greiner, and Markesbery, 2000). Certainly, to be convincing, post-ECT follow-up studies should at least demonstrate improvement in cognitive functioning relative to pre-ECT baseline. As reviewed earlier in this chapter, 2 studies report such improvement: one for mostly non-memory cognitive functions examined 1–2 years following sine-wave unilateral and bitemporal ECT (Abrams and Taylor, 1985) and one for both anterograde and retrograde memory examined 6 months following brief-pulse bitemporal ECT (Calev, Nigal, and Shapira, 1991c).

Because absence of proof is not proof of absence, science cannot prove that ECT of whatever variety is incapable of causing long-term or persistent memory loss. Moreover, there is no *a priori* reason to believe that, under certain circumstances, such an effect cannot occur. It is the task of science to design and carry out further studies of the question, using ever more sensitive and specific measures, with the aim of defining—if indeed they exist—those circumstances under which long-term or persistent dysmnesia might be induced by ECT. Until and unless those studies are performed, and their results found to be confirmatory, all claims that ECT can induce permanent memory loss must receive the Scotch verdict: "*unproved*."

# EXHIBIT 29

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# An Historical Review of Electroconvulsive Therapy

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# An Historical Review of Electroconvulsive Therapy

**Bruce A. Wright, M.D.**

The initial clinical trial of electroconvulsive therapy (ECT) was performed by Ugo Cerletti and Lucino Bini at the University of Rome in 1938. The following paper will examine both the developments which led to the first trial of ECT, and the use of ECT over the subsequent fifty years. Hopefully, by investigating the historical aspects of the development and progression of ECT, a better understanding of this treatment modality can be attained.

The therapeutic use of electricity was not unique to ECT. There is evidence that Ancient Romans used the current generated by electric eels for the treatment of headaches, gout, and to assist in obstetrical procedures. The recent history of the therapeutic use of electricity dates to 1744 when the journal entitled "Electricity and Medicine" was first published. It was claimed here that electric stimuli could be curative for "neurologic and mental cases of paralysis and epilepsy (1)." J.B. LeRoy in the 1755 edition of "Electricity and Medicine" detailed a case of hysterical blindness which was cured with three applications of electric shock (1). In 1752, Benjamin Franklin recorded the use of an "electro static machine to cure a woman of hysterical fits (2)." By the mid 19th century the use of electrotherapy had so progressed that G.B.C. Duchenne (often referred to as the Father of Electrotherapy) would say, "No sincere neurologist could practice without the use of electrotherapy (1)."

But, despite the documented use of electrotherapy through the 19th century, there is little evidence that this was of any influence in the development of ECT. The historical emphasis in the medicinal use of electricity was on the electric stimulus in and of itself, whereas the electricity in ECT was used solely for its convulsant properties.

A more important contribution to the development of ECT was the work of Julius Wagner-Jauregg. It was a common observation in the late nineteenth century that a wide variety of disorders often improved clinically following febrile episodes. Wagner-Jauregg, in 1917, attempted to alleviate the symptoms of dementia paralytica (neuro-syphilis) by inducing fever with the intramuscular injection of blood from patients with malaria. Of the first nine patients he investigated, three had a complete recovery, three had a temporary symptom-

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atic relief of symptoms, and three had no clinical change (3). With this, Wagner-Jauregg essentially opened the door for the biological therapy of mental illness.

The 1930's were an exciting time in the treatment of schizophrenia. Three therapies,—all extrapolations of Wagner-Jauregg's theory—were developed within a several year period. These included: insulin induced hypoglycemia, pharmacologically induced convulsive therapy, and leukotomy. The first of these was Manfred Sakel's insulin induced hypoglycemia. Although the hypoglycemia induced by Sakel occasionally resulted in convulsion, he did not believe that the convulsion was therapeutically necessary. Rather, Sakel felt that the hypoglycemia restricted the activity of that portion of the central nervous system which was responsible for the psychopathology (4).

Sakel's technique was followed in 1934 by Ladislas Meduna's pharmacologically induced convulsive therapy, which will be discussed later. Then, in 1936, Egas Moniz developed the technique of leukotomy (lobotomy) for the treatment of psychosis. Moniz was later awarded a Nobel Prize in 1949 for his work on the psychosurgerical treatment on schizophrenia.

Ladislas Meduna, who graduated from the University of Budapest School of Medicine in 1921, attempted to treat schizophrenia by inducing seizures in his patients. This theory was based on what Meduna felt to be a "biologic antagonism between the epileptic state and schizophrenia (5)." Specifically, he observed clinically that patients with schizophrenia frequently had a decrease in their psychotic symptoms after spontaneous seizures. Moreover, based on autopsy findings, Meduna reported that epileptic brains were associated with a "hyperplasia" of the glial system while schizophrenic brains were associated with a "torpor" of this system (3). He therefore proposed that pharmacologically-induced seizures may be of benefit for the treatment of schizophrenia.

However, Meduna commented in his unpublished auto-biography:

> . . . at this time, however, I did not dare to think of curing schizophrenia, partly because . . . to us, schizophrenia was an endogenous, hereditary disease. Both expressions, endogenous and hereditary, meant that the fate of the patient was determined at the moment of conception; the disease anchored in the ovum and sperm; nothing could change that fate (6).

Despite his reservations, Meduna eventually decided to test his theory. On January 23, 1934, he gave an intramuscular injection of camphor oil to a patient who had been in a catatonic stupor for four years. Meduna described the dramatic improvement in this patient with five camphor oil induced seizures:

> . . . on the morning of February 10, 1934, (two days after the fifth injection) for the first time in four years, he got out of bed, began to talk, requested breakfast, dressed himself without any help, was interested in everything around him, and asked how long he had been in the hospital. When we told him that he had spent four years, he did not believe it (6).

After several trials with camphor oil, Meduna switched to pentylenetrazol (Metrazol) as the epileptogenic stimulant because it produced an immediate convulsion. Despite the initial criticism and opposition, pharmacologically-induced seizures remained a preferred treatment modality for schizophrenia until the advent of ECT.

In 1935, Meduna published "Versuche Uber Die Biologische Beeinflussung Des Ablaufes Der Schizophrenie" ("Attempts To Influence The Cause of Schizophrenia By Biological Means") which documented the results of his first twenty-six schizophrenic patients to have pharmacologically induced seizures (7). The results suggested that there did indeed seem to be an antagonistic relationship between schizophrenia and convulsive episodes. Ten of the twenty-six patients reportedly improved while sixteen were without clinical improvement. Of note, the patients who did improve had received, on the average, 6.2 seizures; on the other hand, those who did not improve had an average of only two seizures per patient. Despite these results, Meduna's work was met with much criticism. Meduna, in his autobiography, recalled the reaction of Dr. Karl Schaffer, the department chairman at the University of Budapest:

> . . . he (Schaffer) called me a swindler, a humbug, a cheat . . . how dare I claim that I cured schizophrenia, an endogenous, hereditary disease. He knew what was in my mind—to publish, get newspaper publicity, and make money! "If you dare publish this paper I disown you." . . . this incident was the first shock I received for the discovery of shock therapy (6).

Ugo Cerletti, the chair of the Department of Neuropsychiatry at the University of Rome, utilized Meduna's pharmaco-convulsive therapy for the treatment of his schizophrenic patients. Cerletti, whose laboratory research involved an examination of the histopathologic changes in Ammon's horn of dogs brains following electrically induced seizures, postulated that electricity could be substituted for Metrazol as the convulsive stimulus for the treatment of psychosis. However, Cerletti was reluctant to pursue this theory:

> . . . the idea of submitting a man to convulsant electric discharges was considered as utopian, barbaric, and dangerous; in everyone's mind was the specter of the electric chair (6).

Cerletti's academic peers attempted to dissuade him from electrically inducing convulsions in man. Among the arguments used against his proposal was the idea that transcranial electricity was used to kill pigs in slaughter houses in Rome. However, Cerletti determined, in research he performed at local slaughter houses, that the pigs were actually put into an electrically-induced epileptic coma during which time their necks were slashed. Cerletti found that pigs could actually tolerate a significant voltage across the head without subsequent death.

Lucino Bini, who had no formal training in psychiatry, worked with Cerletti on the technical aspects of electrical convulsions. Bini noted that there was a

high mortality in Cerletti's laboratory dogs following induced seizures. He determined that this was secondary to the Viale method of electrode placement in which the electrodes were placed in the dogs mouth and rectum. This permitted electrical current to travel through the heart and occasionally cause fatal arrhythmias. Bini subsequently initiated experiments with bitemporal electrode placement.

After significant deliberation and animal experimentation, Cerletti and Bini were prepared to attempt ECT in man. In April, 1938 the first ECT was performed by Cerletti and several members of his staff—Bini, Langhi, Acconero, and Kalinowsky. Cerletti described the first patient, a 40 year old schizophrenic:

> . . . He expressed himself exclusively in an incomprehensible gibberish made up of odd neologisms and, since his arrival from Milan by train without a ticket, not a thing had been ascertainable about his identity (8).

Dr. Cerletti described the first ECT as follows:

> . . . as was our custom with dogs, Bini and I fixed the two electrodes well wetted in salt solution, by an elastic band to the patient's temples. As a precaution, for our first test, we used reduced tension (70 volts) with a duration of 0.2 seconds. Upon closing the circuit, there was a sudden jump of the patient on his bed with a very short tensing of all his muscles; then he immediately collapsed on to the bed without loss of consciousness.
>
> The patient presently started to sing at the top of his voice, then fell silent. It was evident from our experience with dogs that the voltage had been held too low (8).

At this point, there was controversy among the observers whether a repeat stimulus at a higher voltage should be attempted. In the midst of this discussion, the patient pleaded, in language that was no longer incomprehensible, "non una seronda! mortifera!" ("not again it will kill me!"). Cerletti decided, against the majority opinion, to repeat the electric stimulus:

> I (Cerletti) had the electrodes reapplied, and a 110 volt discharge was sent through for 0.5 seconds. The immediate, very brief cramping of all the muscles was once again seen; after a slight pause, the most typical epileptic fit began to take place. True it is that all had their hearts in the mouths and were truly oppressed during the tonic phase with apnea, ashy paleness, and cadaverous facial cyanosis—an apnea which, if it be awe inspiring in a spontaneous epileptic fit, now seemed painfully never ending—until at the first deep, stertorous inhalation, and first chronic shutters, the blood ran more freely in the bystanders veins as well: and, lastly, to the immense relief of all concerned, was

> witnessed a characteristic, gradual awakening by step. The patient sat up of his own accord, looked about him calmly with a vague smile, as though asking what was expected of him. I asked him "what has been happening to you?" He answered, with no more gibberish: "I don't know, perhaps I have been asleep (8)."

The initial patient received thirteen more treatments of ECT over a two month period and was discharged in complete remission. Unfortunately, the patient was lost to follow-up after two years; but, he remained symptom free until that time. The first public presentation of ECT was given by Cerletti at the Medical Academy of Rome in May, 1938. ECT gradually gained acceptance for the treatment of schizophrenia across Europe and by 1943 it had crossed the Atlantic and was being used in America.

Although ECT, at its inception, was used primarily for the treatment of schizophrenia, investigators explored the efficacy of this treatment modality for the entire gamut of psychiatric disorders. Within several years, ECT was a relatively common treatment for the affective disorders, especially depression with psychotic features and severe mania. Approximately 15 years after the first trial of ECT, Jarrie estimated, in a paper on the treatment of affective disorders, that one third of the 60,000 hospitalized patients in England and Whales would receive ECT (9).

The use of ECT was not without potential side-effects and complications. Among these problems were a risk of fractures (especially of the extremities and spinal compression fractures), a relatively high degree of psychic distress experienced by the patients, and cognitive changes following treatments. Several advances were made over the subsequent years to alleviate these problems. Bennet, a psychiatrist, was instrumental in determining the muscle-relaxing agent used by South American hunters to paralyze their prey. He was able to use this agent, curare, during ECT and therefore significantly decreased the risk of fractures (10). Succinyl-choline was later substituted for curare because of its improved side-effect profile (11). In addition to muscle relaxants, barbiturates were administered both to decrease the patient's subjective anxiety prior to treatment and to decrease the anxiety associated with paralysis. With respect to the cognitive changes, it was determined that the unilateral, as opposed to bitemporal, administration of the electrical current would still result in a generalized seizure and was less likely to produce cognitive changes. These advances significantly decreased the complications and side-effects associated with ECT.

The use of ECT in the 1940's was flourishing as there was no other effective treatment for psychiatric disorders. However, with the introduction of neuroleptic medication, and subsequently antidepressants, ECT was used with decreasing frequency. The administration of psychotropic medication was less time consuming and certainly did not have the stigma associated with it that ECT did. In

addition, much of the funding for research on the treatment of psychiatric disorders was provided by pharmaceutical companies.

The psychotropic medications were not, however, the panacea that many people had hoped. They did not have 100% cure rate and were also associated with occasional side-effects and complications. Thus, despite the decline in ECT use following the introduction of psychotropic medication, the 1980's saw a gradual resurgence of ECT. In the United States in 1980, 2.5% of all hospitalized psychiatric patients received ECT; and 13% of all patients admitted to a hospital with a primary diagnosis of an affective disorder received ECT (10). While it is difficult, if not impossible, to perform a statistically sound study of the efficacy of ECT, it has been suggested that ECT is at least as effective, if not more effective, in the treatment of depression than psychopharmacologic interventions.

Despite the resurgence of ECT, this continues to be an extremely controversial treatment for psychiatric disorders. The negative aspect of ECT is advanced by movies like *One flew Over The Cuckoo's Nest* and the anti-psychiatry movement. Sources like these often advance the view that ECT is a psychiatric tool of punishment and retribution.

In conclusion, the use of electricity for therapeutic purposes dates to ancient medicine. However, the concept of using electricity as a convulsive agent for the treatment of psychiatric disorders can be directly traced to the pharmacoconvulsive therapies of Meduna. Over the years, significant improvements have been made in the administration of this treatment in order to significantly decrease the associated adverse effects. At the present time, ECT appears to be as effective as pharmacologic interventions for the treatment of psychiatric disorders. But, for many reasons, including the social stigma associated with its use, ECT is most frequently used only as a last line of therapeutic intervention.

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# EXHIBIT 30

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

DEC 3 1984

Somatics, Incorporated
Attn: Richard Abrams, M.D.
910 Sherwood Drive, Unit 6
Lake Bluff, Illinois 60044

Re: K843923
Thymatron ECT device
Dated: September 27, 1984
Received: October 5, 1984
Regulatory Class: III

Dear Dr. Abrams:

We have reviewed your Section 510(k) notification of intent to market the above device and we have determined the device to be substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market your device subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (Act). This device has been placed into the regulatory class shown above, by a final regulation published in the Federal Register. All classes of devices are regulated by the general controls provisions of the Act applicable to all medical devices including annual registration, listing of devices, good manufacturing practice, labeling, and the misbranding and adulteration provisions of the Act; class II devices must also meet present or future performance standards; class III devices will be required to undergo premarket approval at some time in the future.

Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. We suggest you subscribe to this publication so you can convey your views to FDA if you desire and be notified of any additional requirements subsequently imposed on your device. Subscriptions may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Such information also may be reviewed in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857.

This letter does not in any way denote official FDA approval of your device or its labeling. Any representation that creates an impression of official approval of this device because of compliance with the premarket notification regulations is misleading and constitutes misbranding. If you desire advice on the labeling for your device or other information on your responsibilities under the Act, please contact the Office of Compliance, Division of Compliance Operations (HFZ-32), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

Sincerely yours,

Robert G. Britain

Robert G. Britain
Director
Office of Device Evaluation
Center for Devices and Radiological Health

Swartz 4-1-21

Exhibit 15

S 00522

# EXHIBIT 31

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Swartz 4-1-21
Exhibit 16

OCT 26 1995

Dr. Richard Abrams
Somatics, Inc.
910 Sherwood Drive, Unit 17
Lake Bluff, Illinois 60044

Re: K945120
Thymatron 2000 Electroconvulsive System
Regulatory Class: III (three)
Product Code: GXC
Dated: January 27, 1995
Received: February 1, 1995

Dear Dr. Abrams:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Good Manufacturing Practice for Medical Devices: General (GMP) regulation (21 CFR Part 820) and that, through periodic GMP inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal Laws or Regulations.

This letter will immediately allow you to begin marketing your device as described in your 510(k) premarket notification. An FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in any way represent your device or its labeling as being approved by FDA. If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), promotion, or advertising please contact the Office of Compliance, Promotion and Advertising Policy Staff (HFZ-300) at (301) 594-4639. Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or at (301) 443-6597.

Sincerely yours,

Thomas J. Callahan

Thomas J. Callahan, Ph.D.
Acting Director
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

S 00523

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 6 1998

Mr. Timothy Sheehan
Somatics, Inc.
910 Sherwood Drive Unit 17
Lake Bluff, Illinois 60044

Re: K945120
Thymatron™ 2000 Electroconvulsive System
Dated: December 11, 1997
Received: December 15, 1997

Dear Mr. Sheehan:

We have reviewed the information dated December 11, 1997, regarding the 510(k) notification K945120 previously submitted for the device referenced above. We acknowledge the name change of your device from Thymatron™ 2000 Electroconvulsive System to Thymatron™ System IV and Thymatron™ IV. Based solely on the information that you have provided, it does not appear that you have significantly changed or modified the design, components, method of manufacture, or intended use of the device referenced above (see 21 CFR 807.81(a)(3)). It is, however, your responsibility to determine if the change or modification to the device or its labeling could significantly affect the device's safety or effectiveness and thus require submission of a new 510(k). The information you have supplied will be added to the file.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

# EXHIBIT 32

SOMATICS, LLC
720 Commerce Drive, Suite 101
Venice, Florida 34292
www.thymatron.com

USA & Canada toll-free (800) 642-6661
(847) 234-6761
FAX (847) 234-6763
sales@thymatron.com

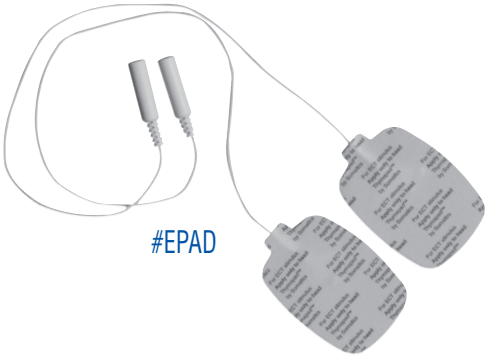






**"Thymatron® System IV: The most advanced ECT device technically and operationally, with demonstrated superior safety and clinical effectiveness."**

# SAFE, TIME-SAVING DISPOSABLES FOR ECT




## THYMAPAD™ Adherent Stimulus Electrodes

*Thymapads*™ are much faster and easier to use than the old-fashioned disk, headstrap, and jelly method.

They remain exactly where applied and have no exposed metal surfaces to cause accidental shocks. There's no mess to clean up afterwards, nothing to wash, dry, or sterilize, no sticky hands - just remove them and discard.

*Thymapads*™ flexibly conform to the surface of the head and fit all Mecta machines too.

## VENTIL-A™ Mouth Protector

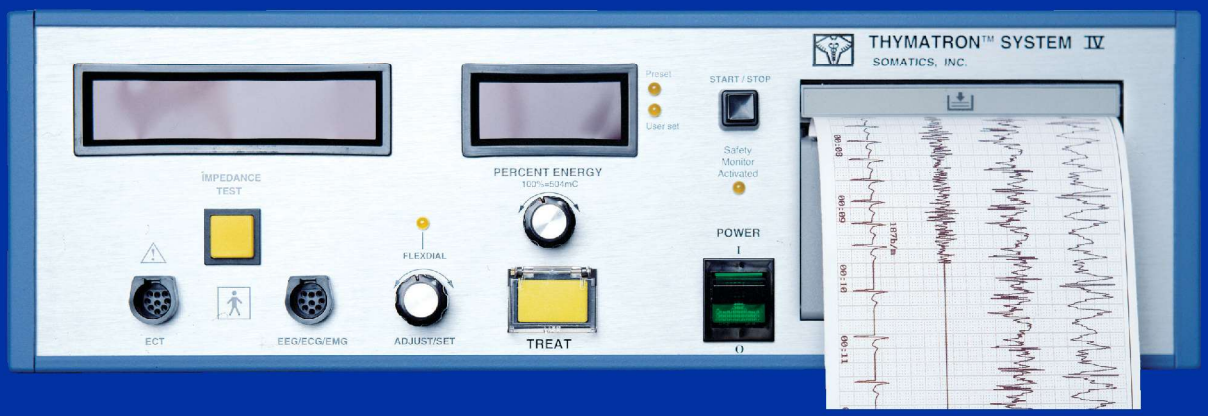
The *Ventil-A*™*'s* thick 100% closed-cell foam construction protects all the teeth. Fits easily under any anesthesia mask and features a non-collapsible air channel for free flow oxygen. One-piece design for dimensional stability and looped end for fast and easy insertion/removal. One size fits >98% of adults.


OVER 1,000,000 SOLD

Both of these single-use ECT aids (US Patent 6039046) save the time and expense of washing and sterilization and eliminate the risk of cross-infection that occurs with re-usable products.

# EXHIBIT 33

# The Streamlined Somatics Thymatron® System Saves Time and Effort




Swartz 4-1-21

**Exhibit 20**

***Your Time is Valuable...Save It With:***

- **Thymapad™ single use stimulus electrodes, for all placements**
- **Ventil-A™ single use compressible mouth protectors**
- **Recording electrodes, single use, for EEG, ECG and EMG**
- **Thymatron® remote treat handle**
- **Steady increment stimulus adjustment for dosing & titration**

***Single use = no cleanup, no sterilization, no contamination.***
***Made for use with Thymatron® System IV.***

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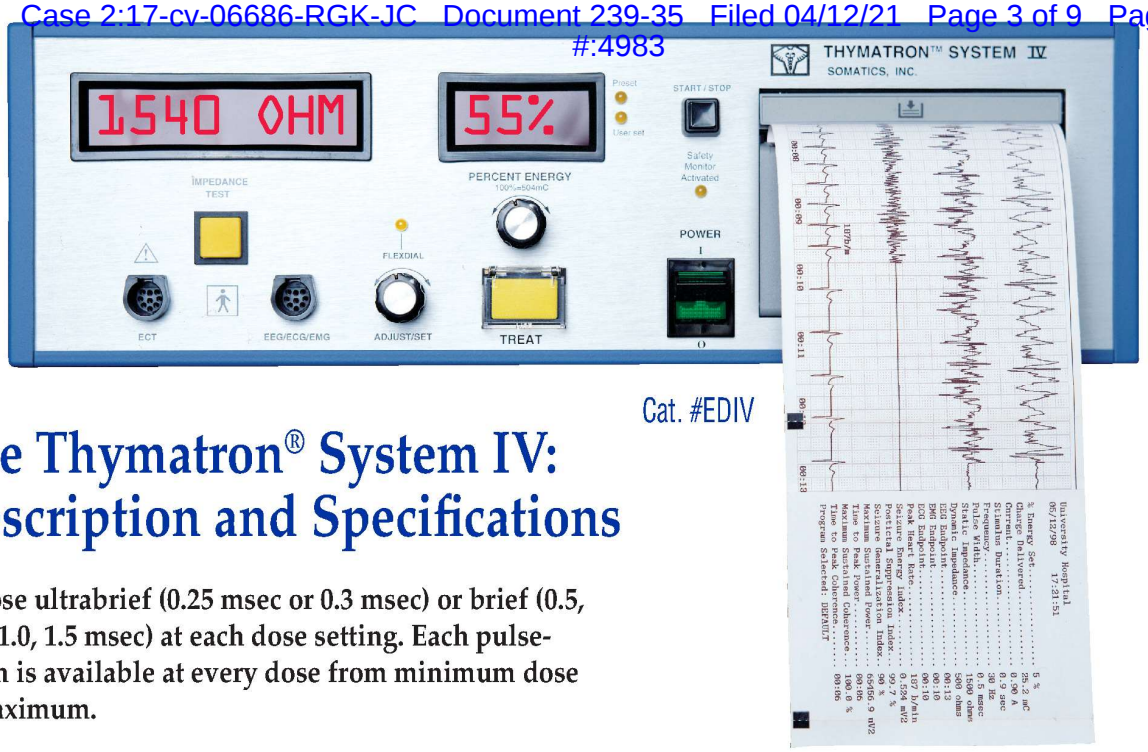


Cat. #EDIV

# The Thymatron® System IV: Description and Specifications

Choose ultrabrief (0.25 msec or 0.3 msec) or brief (0.5, 0.75, 1.0, 1.5 msec) at each dose setting. Each pulsewidth is available at every dose from minimum dose to maximum.

One dial sets the dose. Pulsewidth and frequency are individually assigned for each dose setting. Store your preferences for them in system memory or choose a factory-set group of pulsewidths and frequencies (called "stimulus programs.")

Print your choice of any of these, or change among them as you wish: 1 or 2 channels of EEG alone or with ECG or EMG or both, or 4 channels of EEG.

The Thymatron's 900 mA stimulus current induces seizure at just 60% of the charge needed with 800 mA stimuli. Moreover, greater seizure induction occurs at 900 mA than 800 mA, including at maximum device settings.

About our Ventil-A single-use mouth protectors: "Contemporary disposable foam bite block provides superior protection compared with the rubber bite blocks of the past, as well as increased convenience." – Paparone P, et al. JECT; 35:224.(2019)

- **SINGLE FRONT-PANEL DIAL** lets you select the traditional Thymatron® functions plus important new ones, including *Optimal Stimulus* programs that automatically set the most efficient combination of stimulus parameters at every stimulus dose setting.
- **ELECTRONIC MEDICAL RECORD-KEEPING** is simple with the included Genie™ IV EMR software. Patient treatment records created and stored with the Genie™ IV are easily incorporated into hospital database systems.
- **EXTENDED LOWER STIMULUS RANGE** with pulsewidth and frequency to 0.25 or 0.3 msec and 10 Hz allows you to deliver *stimuli up to 8 seconds long.*
- **EEG COHERENCE MEASURES** *of maximum sustained coherence,* and *time to peak coherence,* interhemispheric cross-correlation measures reported to reflect seizure quality and clinical impact (Krystal & Weiner, 1994; Krystal et al, 1995; Krystal, 1998).
- **EEG AMPLITUDE** measures of *maximum sustained EEG power,* and *average seizure energy,* with separate values for *early, mid–* and *postictal seizure phases,* found by the Duke University group to be important correlates of seizure quality and efficacy ( Krystal & Weiner, 1994; Krystal et al, 1995; Krystal, 1998).
- **HEART RATE MEASURES,** including *peak heart rate,* a key measure of cerebral seizure duration and quality (Larson, Swartz & Abrams, 1984; Swartz, 1993; 1996; Swartz and Manly, 2000) that reflects the autonomic (brainstem) response to ECT. This is supplemented by *digital heart rate* monitoring for safety and seizure generalization, printed each second.

  *All of the above measures are automatically printed.*
- **A POWERFUL 32-BIT INTERNAL COMPUTER** employs *Power Spectral Analysis* to process and store up to 10 minutes of digitized EEG for the special features described here. You can send this data to your IBM PC-compatible computer via a rear-panel serial port for further comprehensive EEG analysis, using Somatics' proprietary Genie™ IV software.

- Because each ECT treatment session is STORED IN MEMORY, you can retrieve it if you run out of paper during a treatment–just slip in another pad after the treatment and *press a button for a complete printout.*

- INDEPENDENT SAFETY MONITOR CIRCUIT prevents the patient from receiving an excessive electrical dose regardless of the operation of the regular circuits.

- TRUE EMG RECORDING OF THE MOTOR SEIZURE. Unlike simple movement detectors, the Thymatron® System IV's EMG can measure seizure muscle activity that is not visible to the naked eye, and which typically continues substantially longer than optically-detectable movements (Couture et al, 1988).

- Because the special computer-automated programs of the Thymatron® System IV are stored on REPLACEABLE MICROCHIPS, updates are easily accomplished on-site via chip replacement. Somatics has already provided 4 advanced microchip upgrades for the System IV including: Genie™ IV computer software, and real-time digital EEG display.

- The POSTICTAL SUPPRESSION INDEX reports the degree of EEG flattening immediately following the seizure, which correlates with clinical efficacy (Nobler et al, 1993; Krystal & Weiner, 1994; Krystal et al, 1995; Krystal, 1998; Nobler et al, 2000). A study of the Thymatron®'s *Postictal Suppression Index* found that it significantly differentiated ECT remitters from non-remitters (Petrides et al, 2000). The authors concluded: *"higher PSI values (more abrupt ending of ictal EEG) are correlated with better clinical outcome of ECT in depression".*

- COMPUTER DETERMINATION AND PRINTOUT OF EEG AND MOTOR SEIZURE DURATIONS. The integral computer EEG analyzer continually measures the EEG and EMG and automatically prints the EEG and motor seizure durations with precision and reliability (Swartz et al, 1994; Krystal et al, 1995).

- JUST SET ACCORDING TO AGE AND TREAT. Setting the Thymatron® System IV according to the patient's age facilitates easy selection of the correct stimulus charge.

- Alternatively, RAPID STIMULUS TITRATION is facilitated with the Thymatron® System IV using a simple method-of-limits procedure (McCall et al, 1993; Rasmussen et al, 1994) that employs research based dose increments: 5, 10, 15, 25, 40, 80, and 100% Energy at your choice of pulsewidth.

(see next page for references)

## THYMATRON® SYSTEM IV FEATURES CHECKLIST[1]

| | Thymatron® System IV | |
|---|---|---|
| Choose 0.25 or 0.3 msec Ultrabrief Pulsewidth | ✔ | ☐ |
| Genie™ IV Software | ✔ | ☐ |
| Four-Channel Monitor/Printer | ✔ | ☐ |
| Stimulus Programs | ✔ | ☐ |
| Maximum Sustained EEG Amplitude | ✔ | ☐ |
| Continuous Digital Heart Rate Monitor | ✔ | ☐ |
| Peak Heart Rate Printout | ✔ | ☐ |
| EEG Coherence Analysis | ✔ | ☐ |
| Seizure Energy Index | ✔ | ☐ |
| Postictal Suppression Index | ✔ | ☐ |
| Maximum Dose Available at all Pulsewidths | ✔ | ☐ |
| Interictal Frontal Delta Analysis | ✔ | ☐ |
| Computer EEG Seizure Duration | ✔ | ☐ |
| Computer Motor Seizure Duration | ✔ | ☐ |
| True EMG Monitor | ✔ | ☐ |
| EEG Ictal Line Seizure Indicator | ✔ | ☐ |
| Light-Emitting Elapsed Time Display | ✔ | ☐ |
| Up to 8 Seconds of Stimulation | ✔ | ☐ |
| Change Waveform without Altering Dose | ✔ | ☐ |
| Audible EEG™ monitor | ✔ | ☐ |
| Instant Impedance Test | ✔ | ☐ |
| Extended Seizure Alert | ✔ | ☐ |
| Patented Safety Monitor Circuit | ✔ | ☐ |

## SPECIFICATIONS

**STIMULUS OUTPUT:**
Current: 0.9 amp constant, limited to 450 volts, isolated from line current.

Frequency: 10 to 70 Hz in 10 Hz increments (to 140 Hz for 0.25 msec pulse).

Pulsewidth: 0.25 or 0.3 msec (choose one) and 0.5 - 1.5 msec in 0.25 msec increments.

Duration: 0.14 to 8.0 sec in increments of equal charge.

Maximum output: Standard maximum output is typically 504 mC current with 99.8 joules energy across 220 ohms impedance. Output for double dose modes (where available) is typically 1008 mC current with 199.6 joules energy across 220 ohms.

**RECORDING:** 8 user-selectable gain positions: 10, 20, 50, 100, 200, 500, and 2000 µV/cm.

**REQUIREMENTS:** 100-130 volts (120 volts) A.C., 60 Hz, single phase. 100 VA. /220-240 volt, 50/60 Hz switchable.

**APPROVALS:** CSA, CE, ISO 13485:2016, IEC 60601

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#EEDS

## SOMATICS' OWN SINGLE USE STICK ON EEG/ECG/EMG ELECTRODES

Easy and quick to use, "the pregelled electrodes provided in the Thymatron DG starter kit. . . reduce preparation time" (Convulsive Therapy 2:53, 1986), compared to metal electrodes and ordinary disposable paper ECG electrodes. They are small enough not to interfere with treatment electrode placement. Ideal for recording EEG, ECG, and EMG, they are conveniently packaged 5 per strip. Instantly adherent, they will remain in place throughout the seizure.

## Updated "Guide to ECT" E-book Gratis

Get your copy of the "Guide to ECT" E-book revised by Conrad Swartz PhD MD. It contains essential written information, according to Dr. Swartz, and is suitable for physicians, residents and nurses. It details organization, patient selection, pretreatment procedures, electrical aspects, electrode placement, anesthesia, monitoring, complications, side effects, and post-ECT considerations.

It's the first ECT guide to include the 2019 FDA ECT regulations ("special controls"). These describe new details of clinical practice the FDA expects ECT practitioners in the USA to know and follow.

For a gratis PDF copy just email a request to *edu@thymatron.com* with your name, degree, city and affiliated hospital name.

#ENSI

## *NEW* REMOTE TREAT HANDLE FOR THYMATRON®

You asked for a remote treat handle and here it is. You can press the TREAT button on this handle instead of reaching over to the Thymatron® itself: a simple thumb press safely triggers the stimulus for any electrode placement, including unilateral.

# A ONE-PAGE COURSE IN ADVANCED ELECTROCONVULSIVE THERAPY

| | |
|---|---|
| % Energy set | 45% |
| % Energy delivered | 45% |
| Charge delivered | 308 mC |
| Current | 0.90 A |
| Stimulus Duration | 7.2 sec |
| Frequency | 70 Hz |
| Pulse Width | 0.3 msec |
| Static Impedance | 1440 ohms |
| Dynamic Impedance | 260 ohms |
| EEG Seizure Endpoint | 48 sec |
| EMG Endpoint | 45 sec |

| | |
|---|---|
| Peak Heart Rate | 128/min |
| Average Seizure Energy Index | 72 $V^2$ |
| Postictal Suppression Index | 96% |
| Maximum Sustained Power | 77841 $\mu V^2$ |
| Time to Peak Amplitude | 33 sec |
| Maximum Sustained Coherence | 95% |
| Time to Peak Coherence | 33 sec |
| Early Ictal Amplitude | 133 µV |
| Midictal amplitude | 264 µV |
| Post-ictal amplitude | 10 µV |

This sample ECT report of the Thymatron® System IV shows that the doctor set the % Energy dial to his patient's age of 45 years, yielding a 308 mC stimulus charge. The *Optimal Stimulus Program* selected a 0.3 msec pulsewidth, 70 Hz frequency stimulus delivered over 7.2 sec. Prior to stimulus administration the impedance measured a safe 1440 ohms, which dropped to 260 ohms during stimulus delivery.

The EEG seizure lasted 48 seconds. Peak seizure amplitude was reached at 31 sec, with a mid-ictal amplitude of 264 *µV, a Maximum Sustained Power of 77841 µV²*, and an *Average Seizure Energy Index* of 72 $V^2$ reflecting strong seizure intensity.

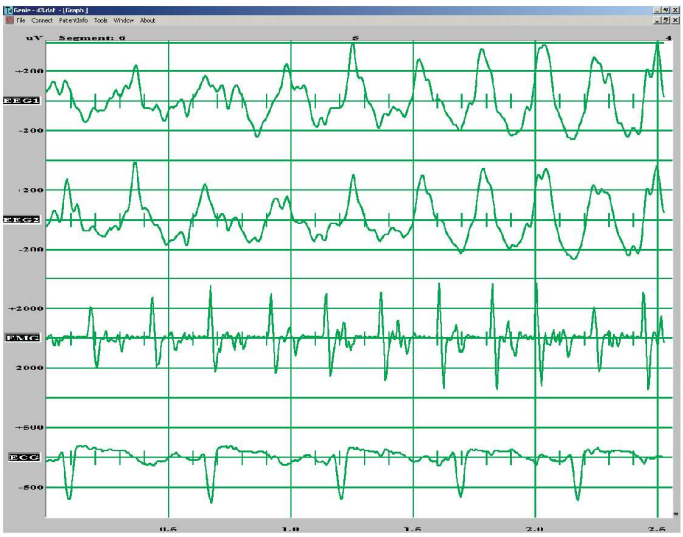
*Peak Interhemispheric Coherence* reached at 33 sec was consistent with the seizure amplitude peak at 31 sec. The *Maximum Sustained Coherence* value of 95% reflected synchronous participation of both hemispheres in the seizure. The rapid drop of EEG seizure amplitude to 10 µV postictally yielded a high *Postictal Suppression Index* of 96%. Power Spectral Analysis was not enabled.

*In summary, the record shows a synchronous, high-intensity, well-developed, and well-generalized EEG seizure pattern with a strong midictal phase, pronounced postictal suppression, and a substantial tachycardia response.*

# GENIE™ IV ELECTRONIC PATIENT DATABASE AND EEG DISPLAY SYSTEM

Designed to meet your clinical and research needs, the Genie™ IV enables you to enter complete patient information at each treatment for storing, printing or incorporating into a hospital-based electronic patient database system.

Equally important is the Genie™ IV's comprehensive real-time display of up to 4 channels of EEG, ECG, and EMG on a PC screen (not included), allowing you to see and then store each treatment session.



*(GENIE™ IV Patient Information Data File/Printout)*

Date: 12-16-05 Name: Laurenz Smarba Age: 58 Sex: M
Somewhat improved but still has insomnia & poor appetite
Oriented, alert, coherent and cooperative
ECT #3 (R-UNI x 1) Anesthesia: Dr. Jones ECT: Dr. Smith
Atropine 0.2 mg - Brevital 50 mg - Succinylcholine 40 mg
Thymatron IV 85% Energy (LOW 0.5 program)
Moderately strong seizure-symmetrical, well developed
Good heart rate response with rapid return to baseline
No complications, quick recovery
Recommendation for ECT #4: same as above

# DOES YOUR ECT DEVICE DELIVER THE DOSE YOU SPECIFY?
# DO YOU TRAIN DOCTORS OR NURSES IN ECT QUALITY?


Device malfunction can cause ineffective ECT treatments or excessive side-effects. Now you can check your ECT device yourself with Somatics' easy-to-use, ECTOBRAIN™II, which performs the same current output check professional engineers use. A single button press instantly tells you if your ECT device is operating safely— providing reassurance and peace of mind. *ECTOBRAIN™II works with any Thymatron.®*

ECTOBRAIN™II also features a Patient Simulator mode that generates EEG, ECG, and EMG signals derived from real patients for testing up to 4 channels of your monitor/printer tracing display and for training and demonstration purposes. Both good- and poor-quality seizures can be selected.

The good-quality seizure shows a high amplitude EEG followed by electrical silence at termination, with a pronounced tachycardia response and a high-amplitude EMG that terminates shortly before EEG termination. The poor-quality recording exhibits a low-amplitude abortive-type EEG seizure lasting only 10 sec, followed by continued but lower-amplitude EEG fluctuations after termination; there is no tachycardia response, and an initial low-amplitude EMG response lasts only a few seconds.

A device checkup can cost $600 to $800 but real costs are more. How often does the question arise in treating a difficult patient whether the ECT device is stimulating properly or the EEG tracing recording correctly? Most ECT *units sent to us for presumed malfunction have nothing wrong with them!* ECTOBRAIN™II can quickly determine whether or not the device is working. It can reveal problems in technique (e.g., recording electrode application) that are correctable on site or with user-replaceable parts (e.g., lead wires). Just connect the stimulus and recording cables and press the TREAT button as for a patient.

The chart recorder of your ECT device will display samples of EEG, ECG, and EMG tracings as described above. The printed report will show the values of the stimulus parameters and other printed variables of your ECT device, including the *measured stimulus charge output* in mC.

*Special price when ordered together with a Thymatron® System IV.*

## Trouble-Shooting with the ECTOBRAIN™II

| *Problem* | *How to test using Ectobrain™II ** |
|---|---|
| No Stimulus output | Section I |
| Impedance test error | Section II |
| ECT stimulus cable failure | Section III |
| No EEG, EMG endpoint | Section IV |
| ECG channel doesn't print | Section IV |
| No Ictal Line | Section IV |
| Special feature doesn't print | Section IV |
| EEG amplifiers require calibration | Section VI |
| ECT stimulus requires calibration | Section VI |

*See specified sections of Ectobrain™ II manual on *www.thymatron.com* downloads page

The *2019 User's Manual for the Thymatron® System IV ECT* device is now available for free download at Thymatron.com. Click "Downloads" in the left column then click "Instruction Manual". It includes these FDA-mandated statements:

- Specific "Instructions to Patients" (see manual Addendum III).
- ECT patients should have cognitive status assessed prior to ECT and along the course with formal neuropsychological assessment (see manual page 11).
- Cautions, warnings and risks, pp 1 and 7-11.
- Review of Thymatron® ECT device efficacy publications, pp 13-15
- Review of Thymatron® ECT device safety publications, pp 15-19
- Specific indications for use of ECT on patients, p6

# MOUTHGUARD ORAL PROTECTORS IN TWO SIZES


#EMGD #EMGS

## SOMATICS THYMATRON® INSTRUMENTS IMPORTANT RESEARCH TOOLS

Since the Thymatron® was first introduced in 1983 hundreds of research studies have appeared in the medical literature using a Thymatron® instrument. Prominent among these is the series of publications by the multi-hospital CORE research group, a consortium of academic psychiatric centers.

In a series of important articles over the last decade the CORE group used Thymatron® ECT instruments to demonstrate the striking efficacy of ECT in the treatment of psychotic depression (Petrides et al, 2001), to determine that age had a strong positive association with the response to bilateral ECT (O'Connor et al, 2001), to show that DSM III melancholic features are unreliable predictors of ECT response (Fink et al, 2007), to find that unipolar and bipolar depressives respond equally well to ECT (Bailine et al, 2010), and to report that, although fewer black than white depressed patients received ECT, there was no overall racial difference in treatment response (Williams et al, 2008).

Hundreds of other studies used a Thymatron® instrument to demonstrate, among other things, that:

ECT given twice a week was equally effective as three times a week, but with fewer cognitive side-effects (Lerer et al, 1995).

Antidepressant potency of high-dose right unilateral ECT was equal to bilateral ECT (Abrams et al, 1991).

Caffeine lengthened seizure duration but did not change the convulsive threshold (McCall et al, 1993).

Bilateral ECT did not yield any evidence for brain damage as measured by levels of neuron-specific enolase and S-100 protein (Agelink et al, 2001).

None of 7 patients with intracranial masses were neurologically adversely affected by ECT (Rasmussen et al, 2007).

In 28 severely depressed patients given a course of unilateral ECT, only responders showed elevations of N-acetylaspartate, suggesting that ECT exhibits positive neurotrophic effects (Michael et al, 2003).

In 32 consecutive patients seizure durations automatically reported by the Thymatron instrument correlated highly with determinations made by trained physicians (Rosenquist et al, 1998).

REFERENCES

Abrams R et al (1991) Arch Gen Psych 48:746; Agelink MW et al (2001) J Neurol Neurosurg Psych 71:394; Aten et al (2015) Eur Arch Psych Clin Neuro 265:351; Bailine S et al (2010) Acta Psychiat Scand 121:431; Eranti S et al (2007)Am J Psych 164:73; Fink M et al (2007) JECT 23:139; Lerer B et al (1995) Am J Psych 152:564; McCall WV et al (1993) Am J Psych 150:1543; Michael N et al (2003) Neuropsychopharm 28:270; O'Connor MK et al (2001) Am J Ger Psych 9:382; Petrides G et al (2001) JECT 17:244; Rasmussen KG (2007) J Neuropsych Clin Neurosci 19:191; Rosenquist PB et al (1998) JECT 14:76; Tew el al (1999) Am J Psych 156:1865; Williams MD et al (2008) JECT 24:117

| | Thymatron | Others |
|---|---|---|
| 2015 | 183 | 137 |
| 2014 | 572 | 369 |
| 2013 | 246 | 149 |
| 2012 | 302 | 179 |
| 2011 | 355 | 222 |
| 2010 | 416 | 255 |

This yield of articles from a 6-year Google Scholar search on the terms *electroconvulsive+year+device* demonstrates that the Somatics Thymatron® is the ECT instrument most preferred by ECT scholars and experts over all other ECT devices.

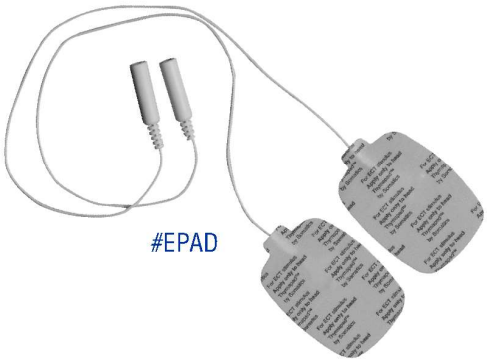
SOMATICS, LLC
720 Commerce Drive, Suite 101
Venice, Florida 34292
www.thymatron.com

USA & Canada toll-free 1 (800) 342-6761
(847) 234-6761
FAX (847) 234-6763
sales@thymatron.com



**"Thymatron® System IV: The most advanced ECT device technically and operationally."**

## SAFE, TIME-SAVING SINGLE USE ITEMS FOR ECT




### THYMAPAD™ Stick-On Stimulus Electrodes

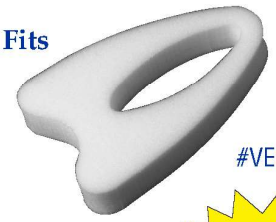
*Thymapads*™ are much faster and easier to use than the old-fashioned disk, headstrap, and jelly method.

They remain exactly where applied and have no exposed metal surfaces to cause accidental shocks. There's no mess to clean up afterwards, nothing to wash, dry, or sterilize, no sticky hands - just remove them and discard.

*Thymapads*™ flexibly conform to the surface of the head.

### VENTIL-A™ Mouth Protector

The *Ventil-A*™'s thick 100% closed-cell foam construction protects all the teeth. Fits easily under any anesthesia mask and features a non-collapsible air channel for free flow oxygen. One-piece design for dimensional stability and looped end for fast and easy insertion/removal. One size fits >98% of adults.




Both of these single-use ECT aids save the time and expense of washing and sterilization and eliminate the risk of cross-infection that occurs with re-usable products.

OVER 1,000,000 SOLD

*ML-TS4, Rev 13*

# EXHIBIT 34

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 550 W. Jackson Blvd., Suite 1500<br>Chicago, IL 60661-4716<br>(312) 353-5863 Fax:(312) 596-4187<br>Industry Information: www.fda.gov/oc/industry | 01/18/2012 - 01/25/2012*<br>FEI NUMBER<br>1420295 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. David L Mirkovich, General Manager/ Sales Manager

| FIRM NAME | STREET ADDRESS |
|---|---|
| Somatics, LLC | 910 Sherwood Dr Ste 23 |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Lake Bluff, IL 60044-2233 | Manufacturer/ Specifications Developer |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

*The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.*

**DURING AN INSPECTION OF YOUR FIRM I OBSERVED:**

**OBSERVATION 1**

Procedures for design validation have not been adequately established.

Specifically,

Your firm's Design Control procedure SOP-0401 has not been adequately established to ensure that design validation is performed on initial production units, lots, batches, or their equivalents. Additionally, your firm's Design Control procedure has not been adequately established to ensure that design changes are validated to conform to defined user needs and intended use of the device. This includes testing of production units under actual or simulated use conditions.

**OBSERVATION 2**

The results of design validation, including method(s), the date, and the individual(s) performing validation, were not documented in the design history file.

Specifically,

Your firm has not documented the results of the design validation for the Thymapad™ stimulus electrode to include the methods, the date, and the individual(s) performing the validation, in the design history file. For example, since January 2008, your firm has made changes to the wire profile inside the Thymapad™ stimulus electrode.

- revision two dated 1/08, indicates to "reduce size of wire fan"
- revision four dated 3/10, indicates "no more fanning of wire"
- revision five dated 3/11, indicates "increased the wire profile inside the electrode to lower immediate current density within the electrode".

**AMENDMENT 1**

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | DATE ISSUED |
|---|---|---|
| | Rafael Padilla, Investigator | 01/25/2012 |



Swartz 4-1-21

**Exhibit 9**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
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| Lake Bluff, IL 60044-2233 | Manufacturer/ Specifications Developer |

There is no documentation in the design history file of the design validation to ensure the device conforms to the defined user needs and intended uses.

**OBSERVATION 3**

The written MDR Procedure does not include an internal system which provides for the timely and effective identification, communication, and evaluation of events that may be subject to medical device reporting requirements.

Specifically,

Your firm's MDR Procedure SOP-1403 Vigillance and Recall does not include an internal system which provides for the timely and effective identification, communication and evaluation of events that may be subject to medical device reporting requirements.

**OBSERVATION 4**

Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established.

Specifically,

Your firm's procedure SOP-1402 Post-Market Communication and Changes is not adequately established so that complaints are processed in a uniform and timely manner, oral complaints are documented upon receipt, and that complaints are evaluated for MDR reportability.

**OBSERVATION 5**

Records of complaint investigations do not include required information.

Specifically,

Your firm's complaint investigations do not include the nature and details of the complaint or any reply to the complainant. For example,

- report log number 110451 documented on your firm's Customer Inquiry/Complaint Form for a Thymatron® system states in the inquiry details "complaining about output, too much energy- not enough energy".
- report log number 111731 documented on your firm's Customer Inquiry/Complaint Form for a Thymatron® system

**AMENDMENT 1**

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| | Rafael Padilla, Investigator Rafael Padilla | 01/25/2012 |

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 OF 5 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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states in the inquiry details "multiple complaints-treating & monitoring".

- report log number 112371 documented on your firm's Customer Inquiry/Complaint Form for a Thymatron® system states in the inquiry details "Doctor had multiple complaints over the last several months".

The investigations do not provide nature and details of the complaints and whether the device was being used to treat a patient. According to your firm's Sales Manager, most of the complaints for the Thymatron® system are associated to some type of issue, real or perceived encountered during treatment of a patient. Additionally your firm does not document any reply to the complainant.

**OBSERVATION 6**

Procedures for acceptance of incoming product have not been adequately established.

Specifically,

Your firm has not adequately established procedures for the acceptance of incoming product to include the documented acceptance or rejection activities of incoming product.

**OBSERVATION 7**

There is no agreement with suppliers to notify you of changes in the product or service.

Specifically,

Your firm does not have an agreement with the suppliers of the Thymapad™ stimulus electrode and the EEDS snap recording electrodes to notify you of any changes in the product or service so that your firm may determine whether the changes may affect the quality of the finished device.

**OBSERVATION 8**

Acceptance activities were not adequately documented.

Specifically,

~~Records for the~~

~~T~~Records for the acceptance activities of the Thymatron®, EEDS recording electrodes, and the Thymapad™ stimulus electrodes are not adequately documented to include the acceptance activities performed and the signature of the Individual(s) conducting the acceptance activities and where appropriate the equipment.

**AMENDMENT 1**

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| | Rafael Padilla, Investigator | 01/25/2012 |

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
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**OBSERVATION 9**

Procedures have not been adequately established to control product that does not conform to specified requirements.

Specifically,

Your firm's Nonconforming Material procedure SOP-1301 does not include how nonconformances will be handled to address the documentation and evaluation of the nonconformance to include a determination for the need for an investigation of the nonconformance.

**OBSERVATION 10**

Procedures to ensure sampling methods are adequate for their intended use have not been established.

Specifically,

Your firm's incoming acceptance activities for the Thymapad™ stimulus electrodes and EEDS recording electrodes requires samples to be inspected from each incoming shipment of product regardless of lot size. Your firm's procedure SOP-2001 Statistical Techniques does not ensure sampling methods are adequate for their intended use.

**OBSERVATION 11**

Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.

Specifically,

Your firm's procedure SOP-2001 Statistical Techniques does not identifying a valid statistical technique for controlling and verifying product characteristics of incoming product and supplies as well as your firm's use of statistics to evaluate complaints associated to a product line or lot of product.

**AMENDMENT 1**

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| | Rafael Padilla, Investigator | 01/25/2012 |

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
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## Observation Annotations

| | | | |
|---|---|---|---|
| Observation 1: | Promised to correct. | Observation 2: | Promised to correct. |
| Observation 3: | Promised to correct. | Observation 4: | Promised to correct. |
| Observation 5: | Promised to correct. | Observation 6: | Promised to correct. |
| Observation 7: | Promised to correct. | Observation 8: | Promised to correct. |
| Observation 9: | Promised to correct. | Observation 10: | Promised to correct. |
| Observation 11: | Promised to correct. | | |

*** DATES OF INSPECTION:**
01/18/2012(Wed), 01/24/2012(Tue), 01/25/2012(Wed)

**AMENDMENT 1**

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | DATE ISSUED |
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| | Rafael Padilla, Investigator | 01/25/2012 |

Inspection ID: 275367
Firm Name: Somatics, LLC

# Non-Printing Observations

**OBSERVATION 1**

Devices for which listing is required have not been listed.

Specifically,

Your firm has not submitted device listings with the specific product codes for the following medical devices: MouthGuard/ Ventil-A™ Mouth Protector and Thymapad™ stimulus electrode/ EEDS recording electrodes.

# EXHIBIT 35

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Attorneys for Plaintiffs JOSE RIERA;
And DEBORAH CHASE

**UNITED STATES DISTRICT COURT**

**CENTRAL DISTRICT OF CALIFORNIA**

JOSE RIERA and DEBORAH CHASE,

Plaintiffs,

v.

SOMATICS, LLC

Defendant.

Case No.: 2:17-cv-06686 RGK(PJWx)

Action Filed: September 11, 2017
Trial Date: October 2, 2018
Assigned: Hon. R. Gary Klausner
Courtroom: 850

**DECLARATION OF NANCY A. PRESSLY**

I, Nancy A. Pressly, declare under penalty of perjury as follows:

1. My name is Nancy A. Pressly. I am employed as the Associate Division Director, Division of Post-Market Surveillance, Office of Surveillance and Biometrics, Center for Devices and Radiological Health (CDRH), U.S. Food and Drug Administration (FDA). I have been employed by the FDA since 1987. In the course of my duties at the FDA, I have become familiar with the FDA's System for

Uniform Surveillance (SUS) and the CDRH Ad Hoc Reporting System (CARS).

2. In this capacity, and pursuant to a civil subpoena, I was asked to conduct a search of SUS and CARS to locate, amongst other documents: "All communications between Somatics, LLC and the FDA regarding any reporting of adverse events using ECT devices, for the period from 1979 to the present."

3. This search has now been completed to the satisfaction of the FDA.

4. As a diligent search, and having made all reasonable inquiry into the matter, I have confirmed that the FDA has no record of Somatics, LLC ever having filed any adverse event reports to the FDA relating to ECT devices at any time.

I declare under penalty of perjury the foregoing is true and correct. Executed this 2nd day of July, 2018 at White Oak, Maryland.

Nancy A. Pressly

# EXHIBIT 36

# 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 |

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| | | 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<br>Benton: NSS initially, SS improved at 30 days, NSS at 1 | PALT BL worse initially, NSS by 10 days<br>Benton: NSS<br>Personal Data Sheet: BL worse after ECT 6—SS | UL less memory impairment initially but required more treatment sessions for response |

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| | | | | | | | year<br>Personal Data Sheet: SS declined over course of ECT | | |
| Chanpattana | 1999 | Treatment resistant SCZ | 51 (45 compl eted) | 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;<br>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;<br>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;<br>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<br>(6/8 ECTs) | Acute; 24 hrs. after ECT 8; 4-6 weeks | Confusion clinician rating;<br>MWLT;<br>Graham-Kendall;<br>Benton;<br>WMS<br>Part I—Personal and Current Info | NST all measures | Confusion: BL worse—SS<br>MWLT:<br>ULND best at 4-6 weeks only—SS<br>WMS Personal: ULND best at 24 hours and 4-6 weeks—SS<br>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;<br>Placebo group immediate memory— | Face: forgetting score worse L-TP—SS<br>All others— NSS | Memory possibly worse with L-TP |

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| | | | | | | 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 | |

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| | | | | | | associate learning, WMS-VR | weeks—SS<br>WMS-MC: both improved at 3 weeks—SS<br>Memory passage: ULND improved at both times—SS<br>Associate learning, VR: BL improved at both times—SS<br>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<br>Famous names: sham worse acutely—SS<br>All others NSS | Word list recognition at 2 days: real ECT worse—SS<br>Face label real worse acutely—SS<br>Sentence verification, famous names: sham worse acutely—SS<br>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<br>Patient endorsed memory problem: both declined at 6 months—SS<br>All others NSS or NST | Word list recognition: real worse—SS<br><br>Sham ECT worse at 1 month—SS<br><br>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<br>Digit span: LUL worse than RUL at 2 days, BL worse than RUL at 3 months—SS<br>Verbal learning: LUL worse | |

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| | | | | | | | | than RUL/BL at 2 days, worse than RUL at 3 months—SS<br>Non verbal learning: LUL worse than RUL at 2 days and 3 months—SS<br>Delayed nonverbal: BL worse than RUl at 3 months—SS<br>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<br>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<br>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<br>WMS-ss, CFT: BL declined—SS<br>All others NSS | Digits backward, random numbers, PALT, WMS-ss, CFT: BL worse—SS<br>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, | |

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| | | 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<br>Williams declined acutely—SS<br>All others NSS | Williams acutely only—SS<br>WVLT: BL/LUL worse than RUL—SS<br>WMS-VR: BL worse than control—SS<br>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<br>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<br>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<br>RAVLT: BF worse than BT—SS<br>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<br>Pauli: ISONAR improved—SS<br>GVM-A: both improved—SS<br>GVM-C: ISONAR improved, BT declined—SS<br>Benton: ISONAR | ACOT variability, GVM-C: BT worse—SS<br>All others NSS | |

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| | | | | | | | same, BT improved—SS<br>All others NSS | | |
| Levy | 1968 | depression | 40 | UL vs. BL<br>(6 ECTs) | 6 hours after last ECT | Gresham-GO +GE + RPE, WMS, PALT, | All declined—SS | All groups NSS<br>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;<br>controls same—NSS<br>PIMT-P: ECT declined;<br>controls same –SS | All measures: BL worse--SS; dose no effect—NSS | |
| Martensson | 1994 | MDD DSM-III (47), other (6) | 53 | ECT propofol<br>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<br>WMS 24 hour recall, ROCF copy decreased acutely—SS<br>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<br>Subjective memory #9-16 improved—SS<br>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<br>Porteus—NSS | WMS: 3x/week worse—SS<br>Porteus—NSS | |
| McCall | 2002 | MDD; no SCZ, SCZ-AFF, substance abuse, MR, or neuro problems | 77 | RUL 8x threshold vs.<br>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.<br>Duke:<br>Fixed high dose worse— | |

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| | | | | | others | CFT, Duke, patient memory rating scale | | SS<br>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<br>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<br>All others: NST | WMS, autobio questions: NSS<br>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.<br>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<br>All others NSS for RUL vs. | |

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| | | | | 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<br><br>All others NST | Time to reorientation, paired words: BL, high dose worse--SS<br>SRT, MMSE, AMI:<br>BL worse—SS<br>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<br><br>All others NST | Time to reorientation: RUL high worse than RUL low/med; BL worse than any RUL—SS<br>mMMSE, BSRT, paired words, Randt picture recall, famous events, AMI: BL worse—SS<br>Randt short story, CFT: High dose RUL + BL worse than low/ mod RUL--SS<br>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<br>All others NST | Time to reorientation: Brief pulse worse vs. UBP--ss; BL worse vs. RUL—SS<br>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<br>MMSE, BSRT, CFT: Brief pulse worse vs. UBP at 1 week—SS<br>Randt story recall, Goldberg Barnett, AMI, patient memory rating: Brief pulse worse at 1 week--ss; BL worse at 1 week--ss<br>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 | |

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| | | 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<br>Global battery at 1 month: NSS | backward,retrograde word list: 3x/week worse at 3 days—SS<br>Verbal + verbal vs visuospatial recall, delayed visuospatial recall subtests:<br>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<br>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<br>AMI: C-pharm improved at 12 weeks only—SS<br>SSMQ: both improved at 24 weeks only—SS<br>All others NSS | AMI: C-ECT worse at 12 weeks only—SS<br>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<br>Others NSS or NST | Time to reorientation: BL worse—SS; high dose worse—SS<br>MMSE (acute + 1 week), AMI ( 1 week): BL worse—SS<br>Dose comparisons: NSS | |
| Stoppe | 2006 | MDD<br>Age >60 | 39 | RUL vs. BL modified fixed high dose | 1day, 1 month | MMSE, digits forward + backward, WAIS-R vocabulary, | MMSE: NST<br>All others NSS | MMSE at 1 day: BL worse<br>All others (at 1 month): NST | |

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| | | | | | | 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<br>Benton: NSS | PALT: BL worse—SS at 36 hours, NSS at 10 days<br>Personal data sheet: BL worse at 36 hours--SS, NST at 10 days<br>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<br>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<br>Age 45+ | 15 | BT + propofol interruption post seizure vs.<br>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<br>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<br>Logical memory at 2 weeks only: High sine improved— SS; high pulse improved on 1 | All NSS | |

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| | | | | | | | story—<br>SS<br>Verbal recognition at 2 weeks: high sine improved—<br>SS<br>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;<br>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:<br>BL and sine worse than controls—<br>ss<br><br>Famous events at 2-3 days: BL worse than controls—<br>SS<br><br>CFT at 2-3 days: BL, ULND, and sine worse than controls—SS<br><br>All NSS at 6 months except: personal memory declined—SS<br><br>All others NSS | VPA, famous events, famous faces, personal memory at 2-3 days:<br>BL worse—SS; Sine worse—<br>SS<br><br>WMS-P at 2-3 days: BL worse vs. control—SS; sine worse—<br>SS<br><br>CFT at 2-3 days: sine worse—<br>SS<br><br>All NSS at 6 months except personal memory: BL worse; sine worse vs. controls—<br>SS<br><br>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:

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

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

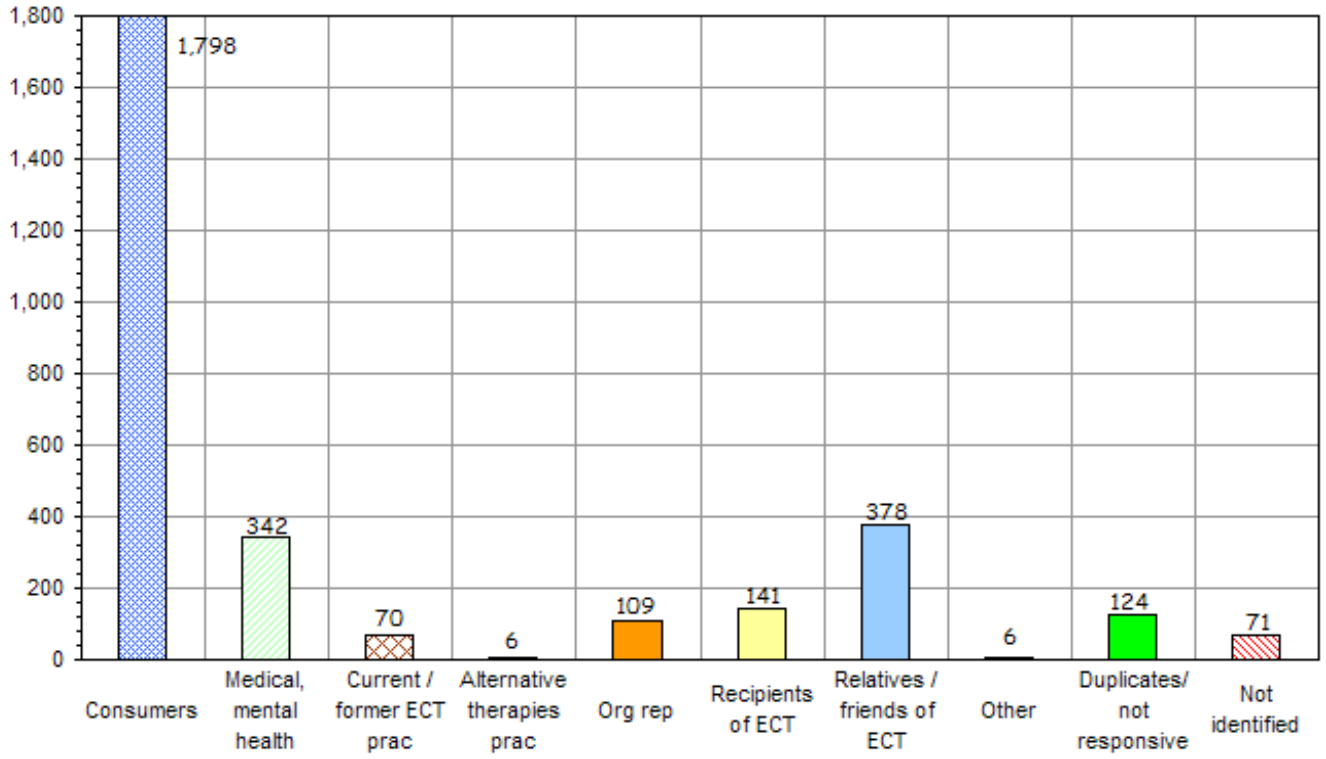
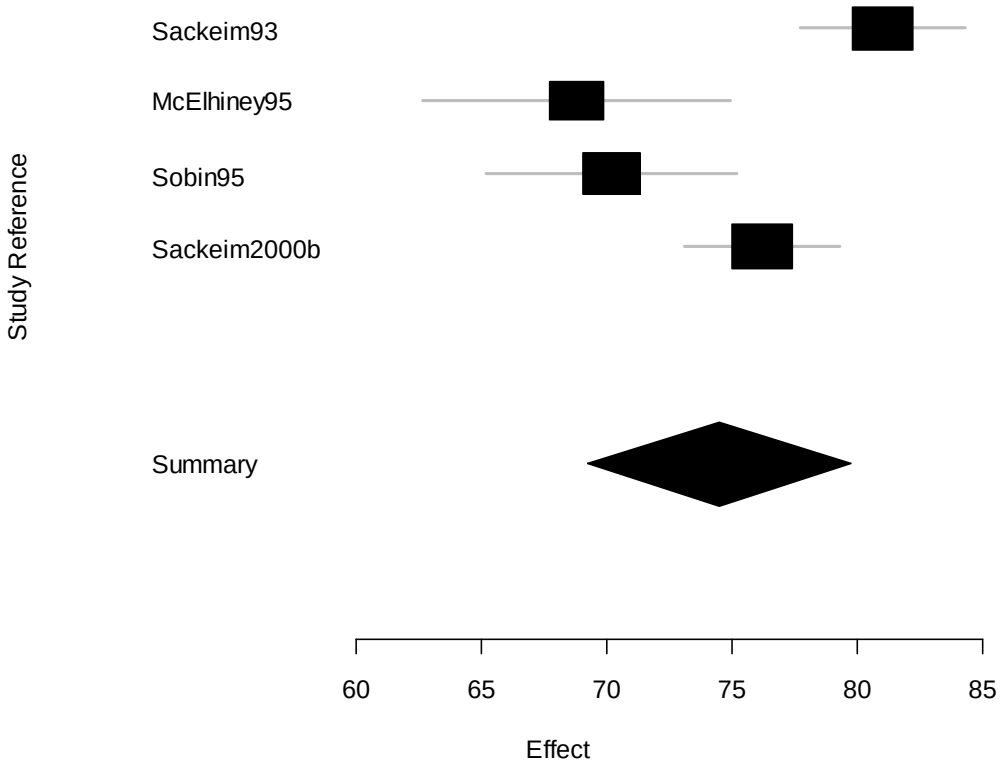


**Figure 2. Meta-Analysis: Autobiographical Memory Right Unilateral Low Energy ECT (pre-post % recall)**

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| | 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 |

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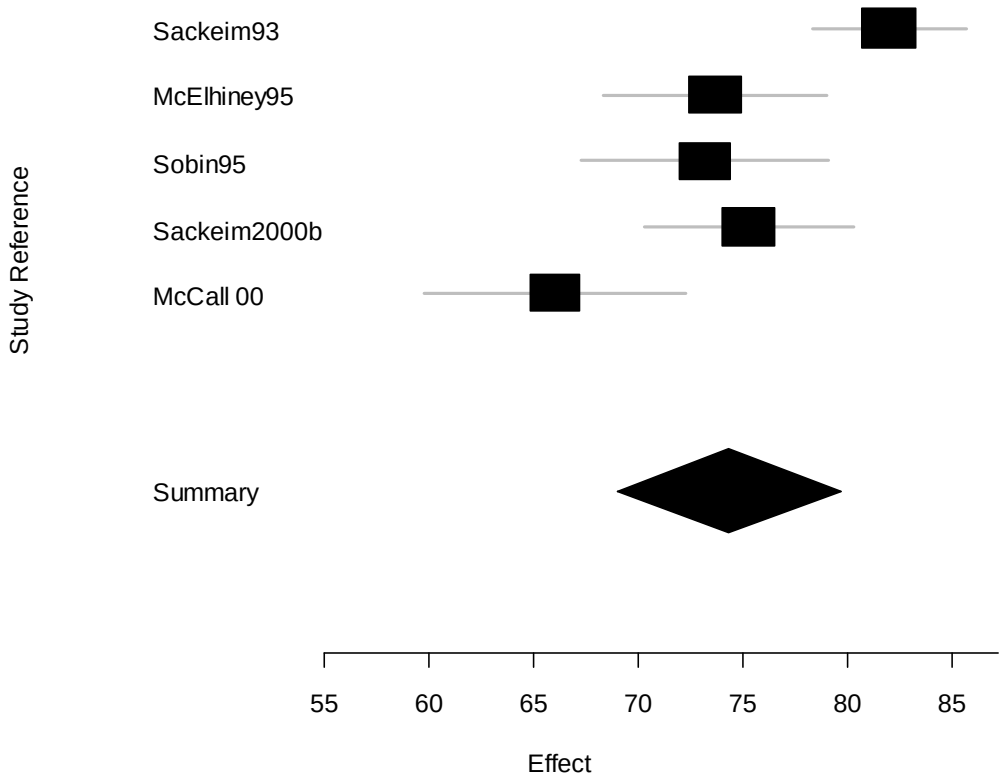
Summary effect: **74.49** 95%CI( 69.24, 79.73 )

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

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| | 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 |

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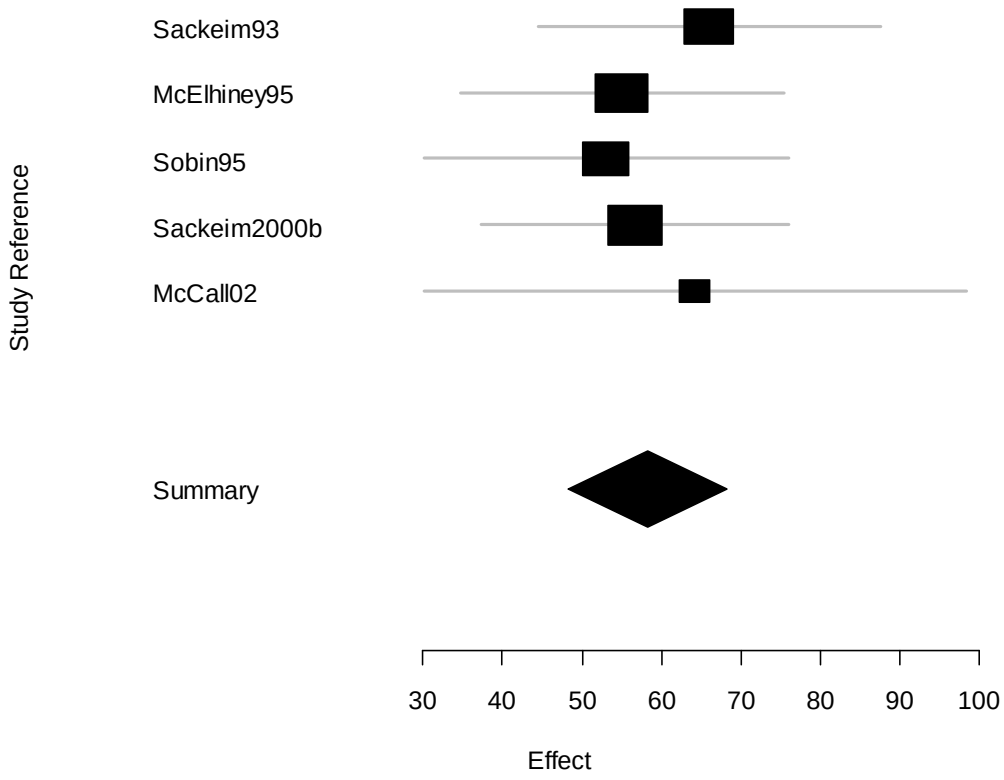
Summary effect: **74.35** 95%CI( 69.02, 79.68 )

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

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| | 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 |

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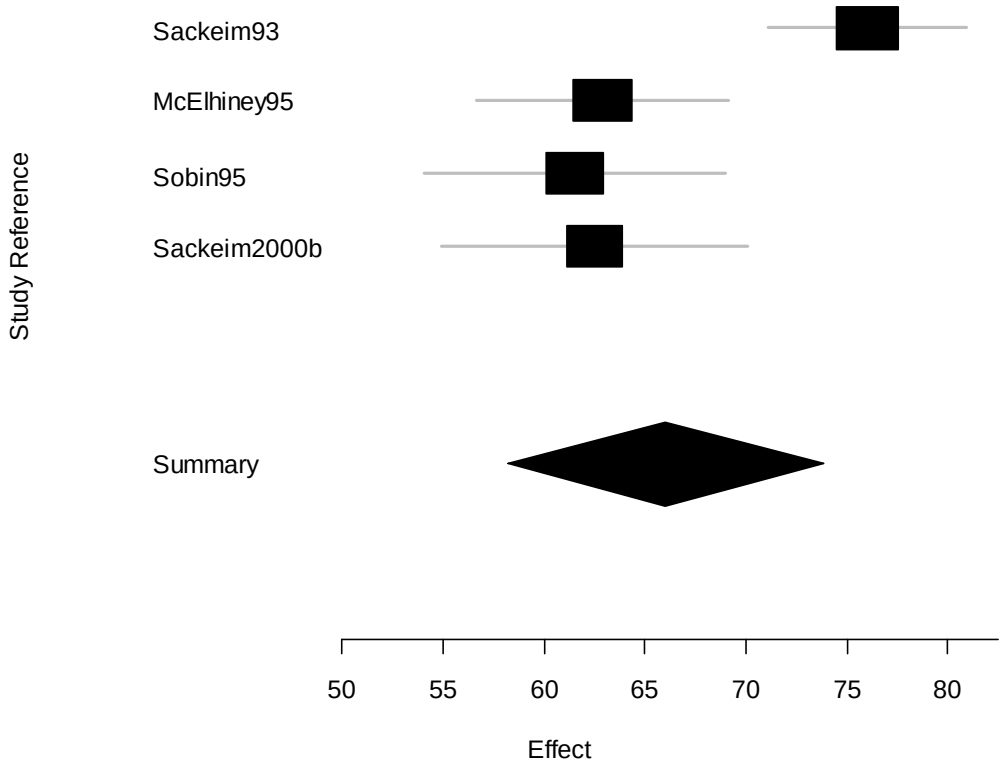
Summary effect: **58.24** 95%CI( 48.22, 68.25 )

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

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| | 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 |

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

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

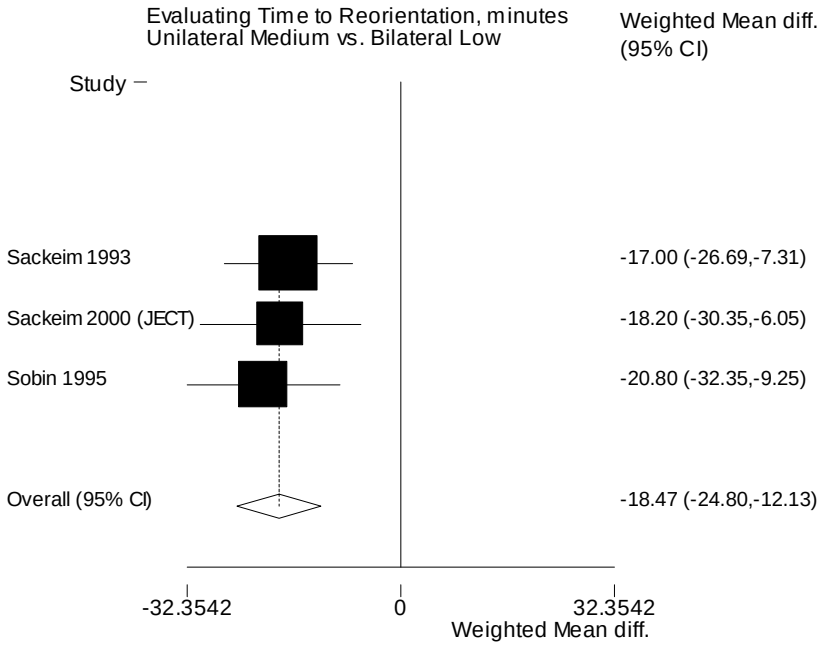


**Figure 7. Time to Reorientation (minutes): Unilateral Medium vs. Bilateral High**

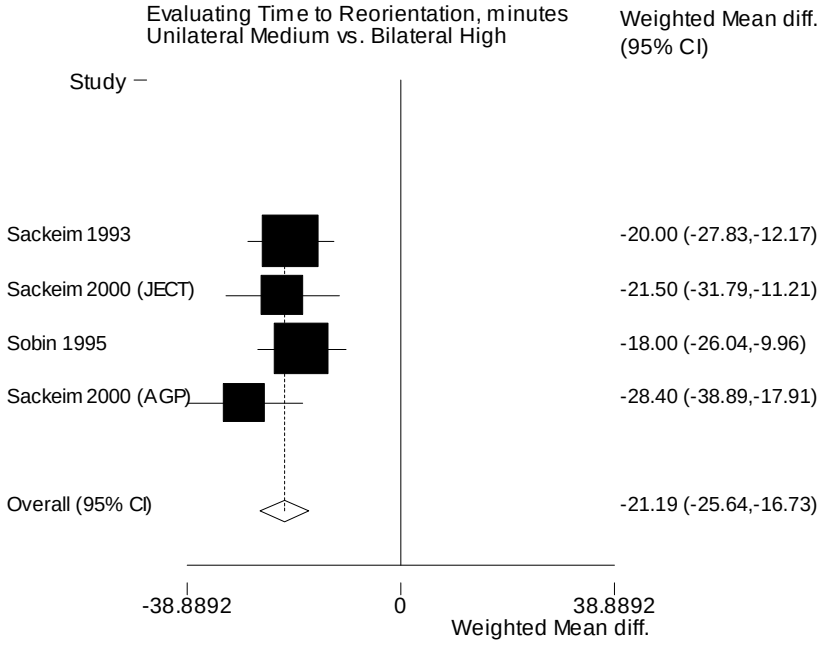

**Figure 8. Time to Reorientation (minutes): Unilateral Low vs. Bilateral High**

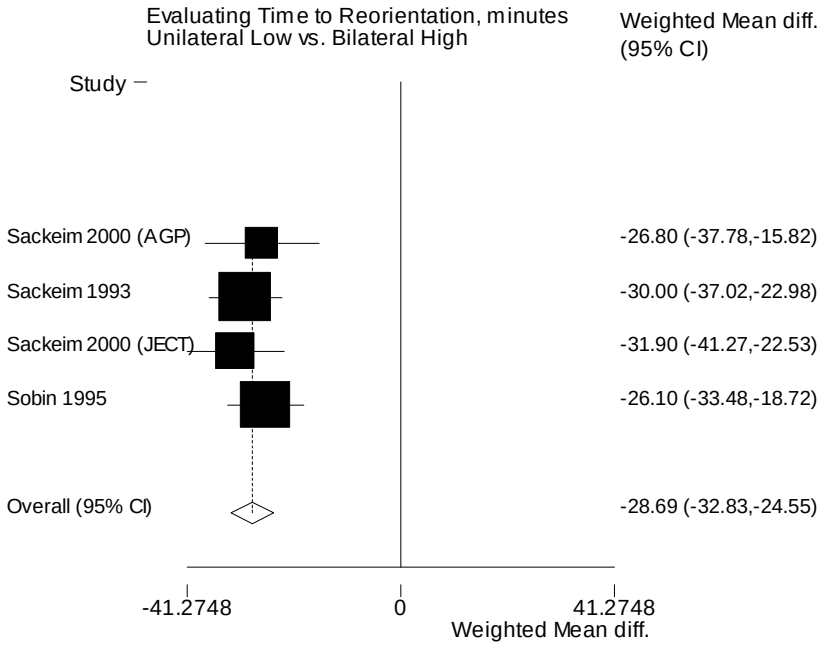


**Figure 9. Time to Reorientation (minutes): Unilateral Low vs. Unilateral Medium**

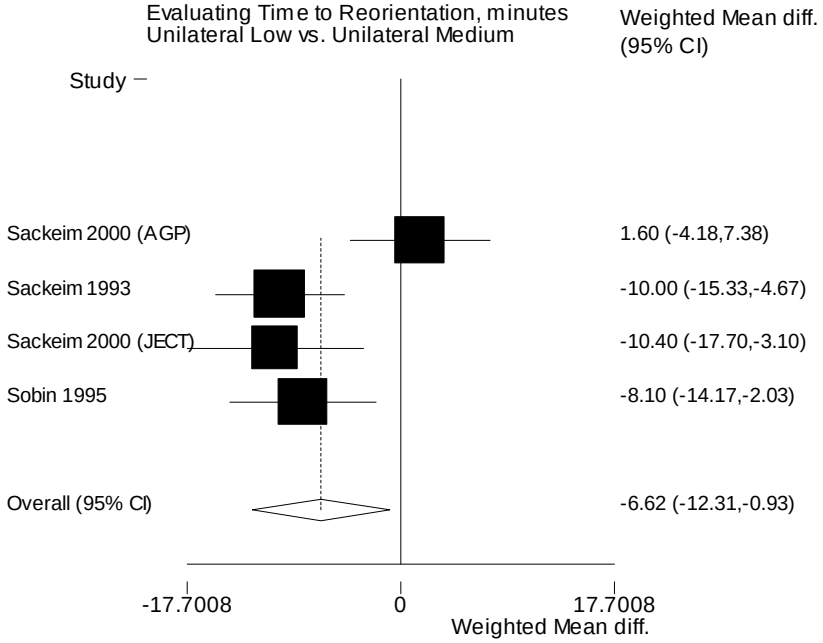

**Figure 10. Time to Reorientation (minutes): Bilateral Low vs. Bilateral High**

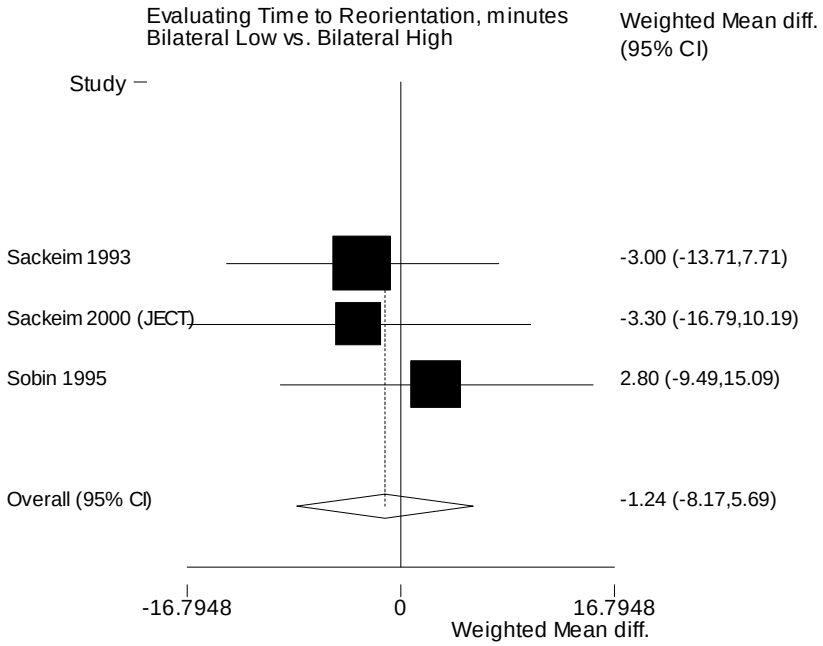

**Figure 11. MMSE Immediately Post-ECT: Unilateral Medium vs. Bilateral Low**

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.

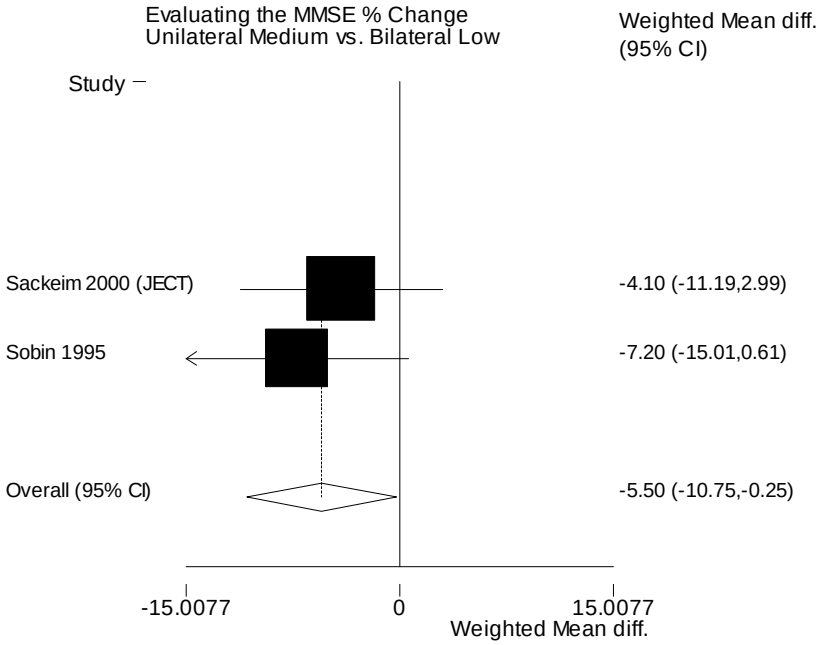

**Figure 12. MMSE Immediately Post-ECT: Unilateral Medium vs. Bilateral High**

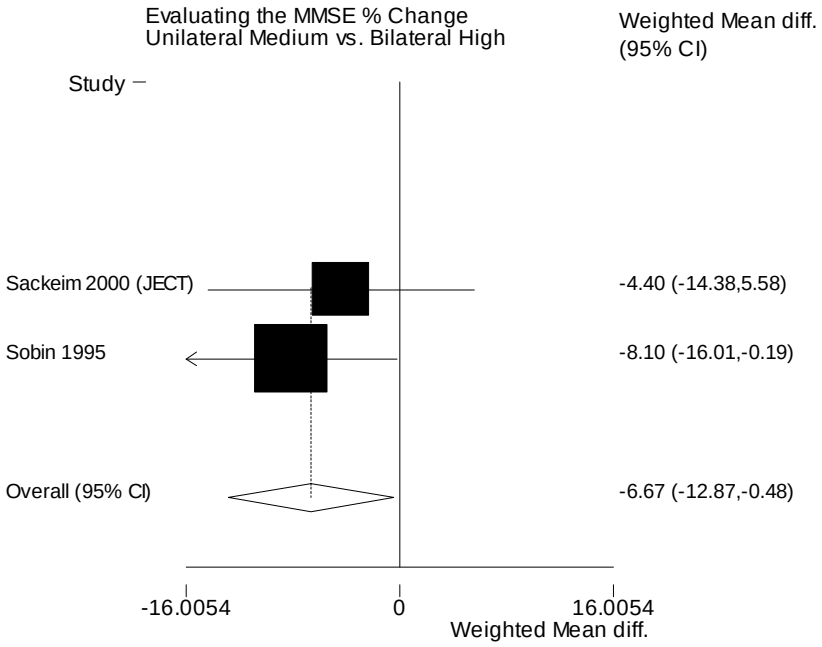


**Figure 13. MMSE Immediately Post-ECT: Unilateral Low vs. Bilateral High**

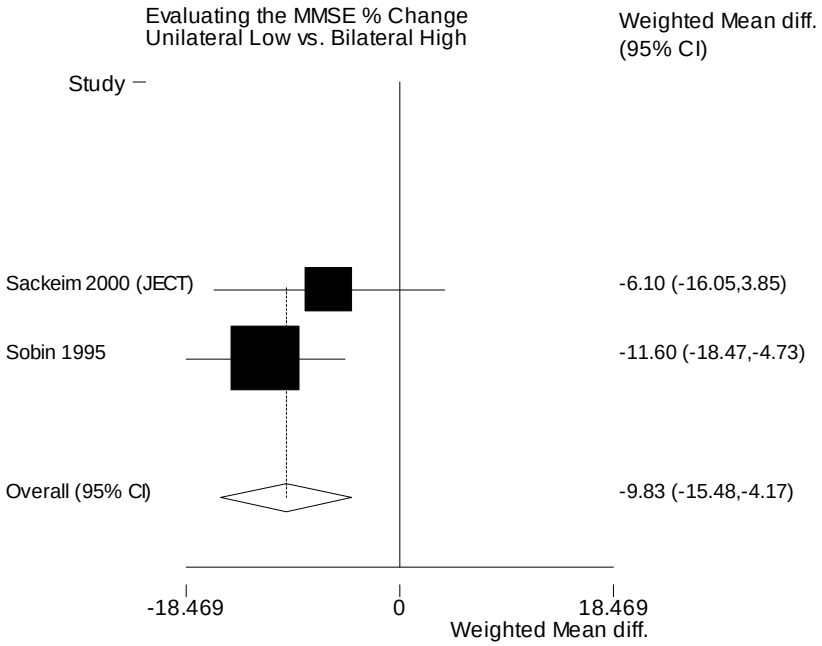

**Figure 14. MMSE Immediately Post-ECT: Unilateral Low vs. Unilateral Medium**

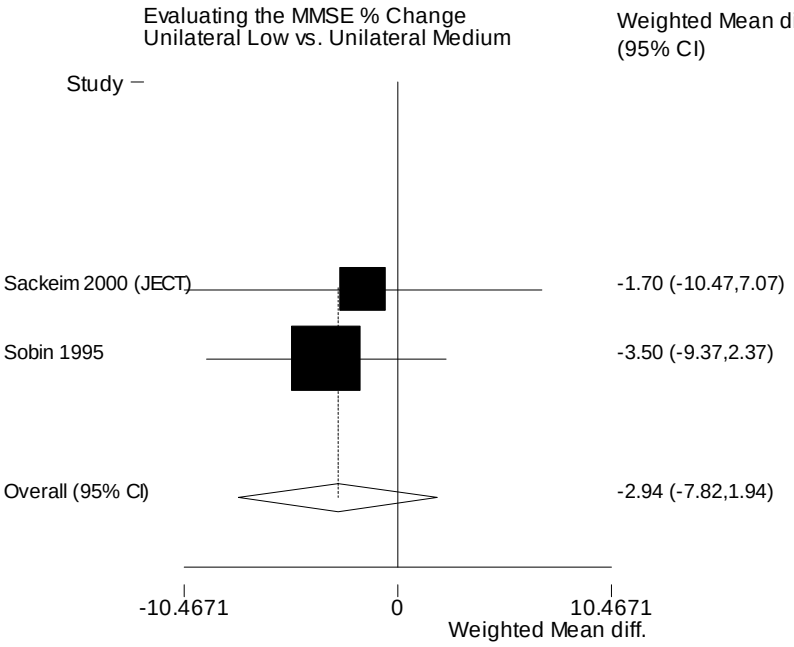


**Figure 15. MMSE Immediately Post-ECT: Unilateral Low vs. Unilateral Medium**

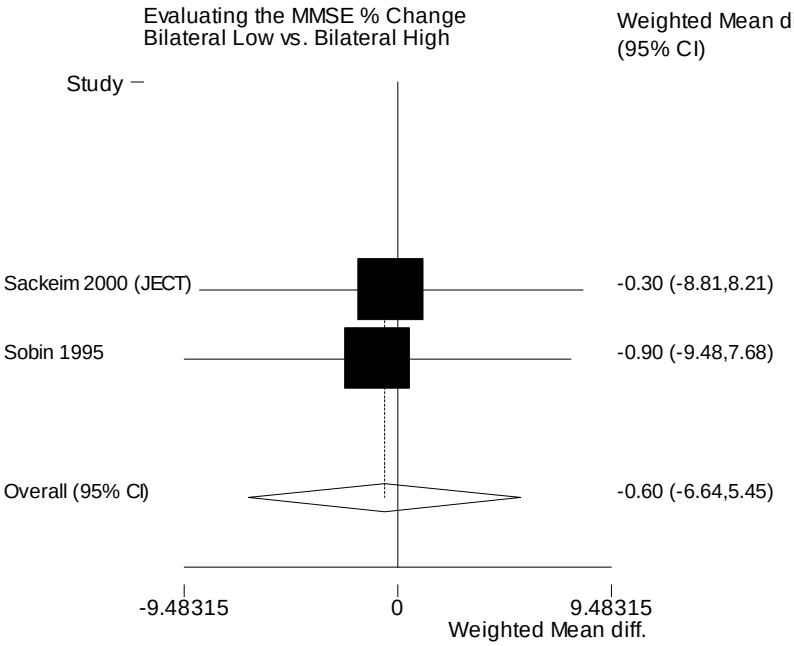

**Figure 16. MMSE 2 Months Post-ECT: Unilateral Medium vs. Bilateral High**

Meta-analysis MMSE at 2 months post-course

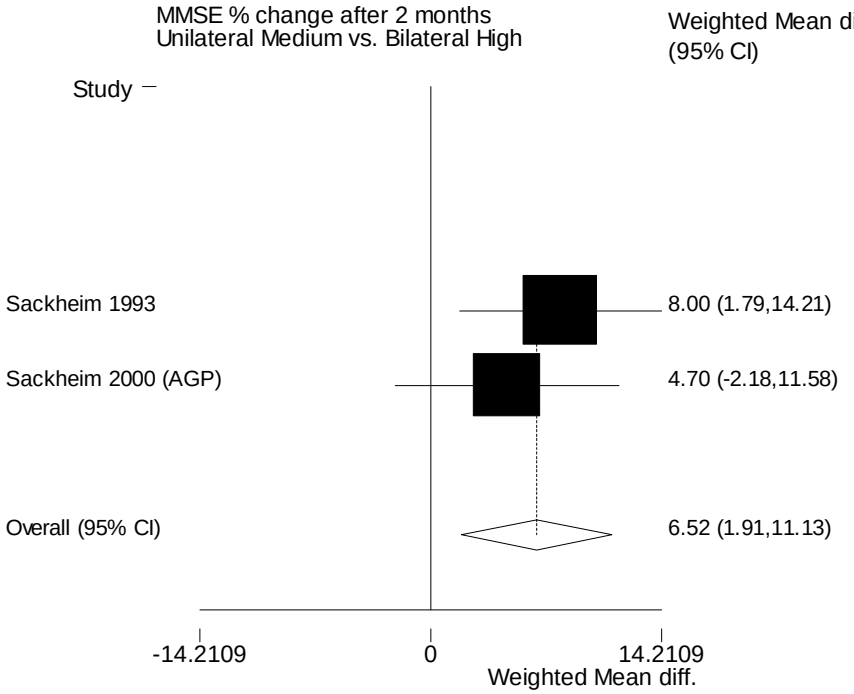

**Figure 17. MMSE 2 Months Post-ECT: Unilateral Low vs. Bilateral High**

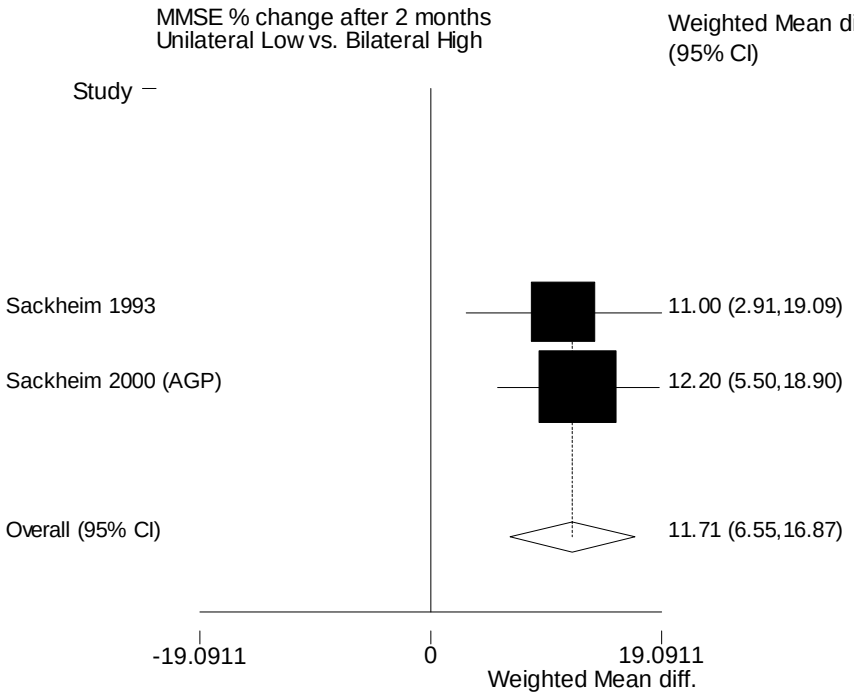


**Figure 18. MMSE 2 Months Post-ECT: Unilateral Low vs Unilateral Medium**

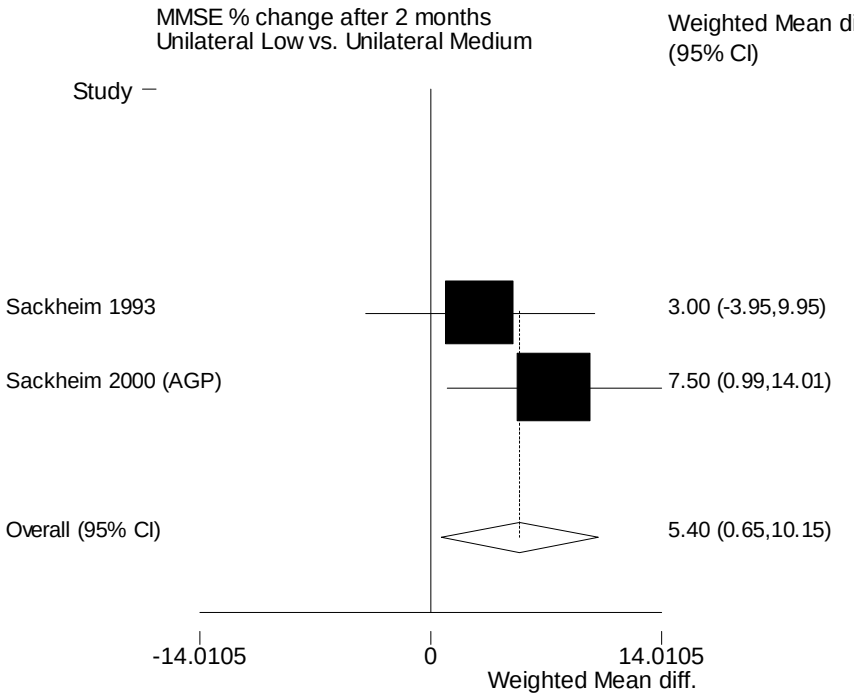

**Figure 19. AMI Sub-Acute (1 Day – 1 Week): Unilateral Medium vs. Bilateral Low**

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.

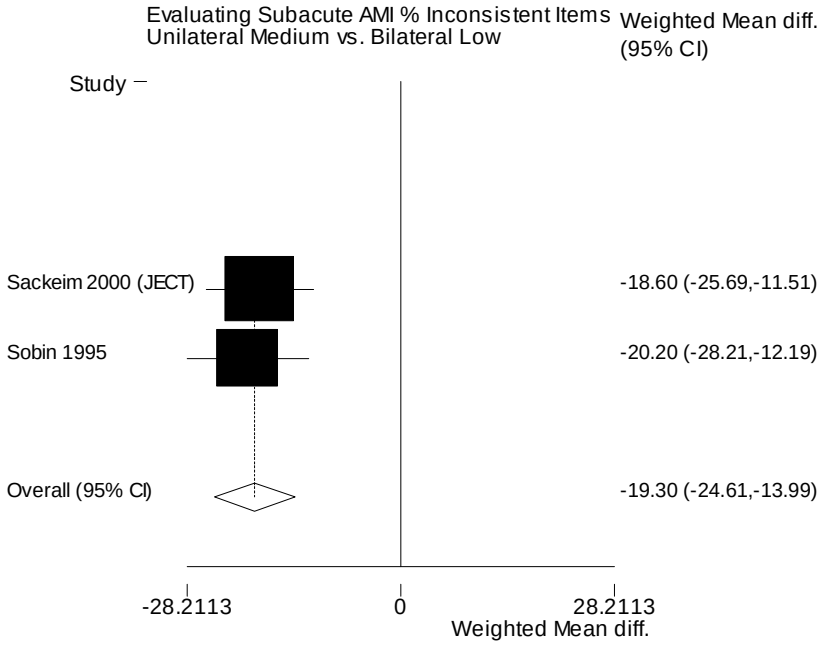

**Figure 20. AMI Sub-Acute (1 Day – 1 Week): Unilateral Medium vs. Bilateral High**

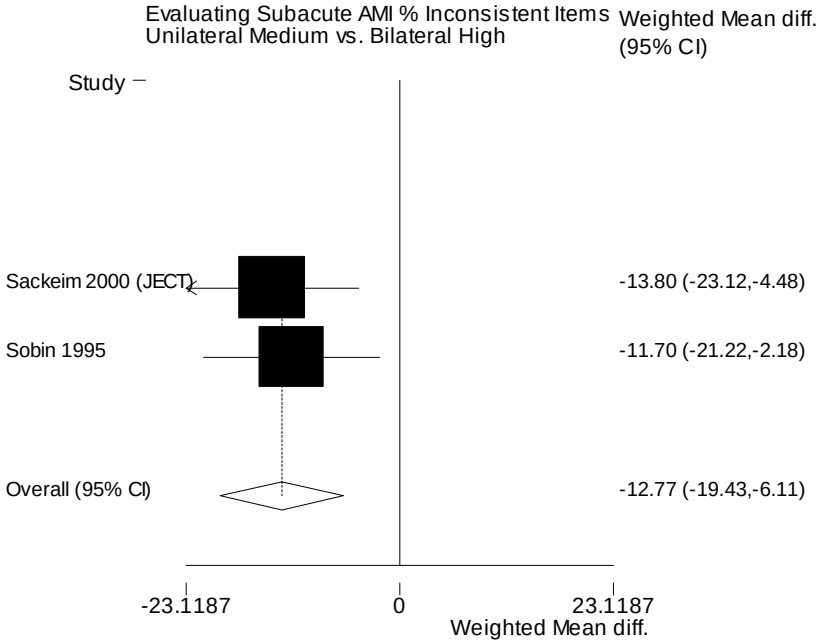


**Figure 21. AMI Sub-Acute (1 Day – 1 Week): Unilateral Low vs. Bilateral High**

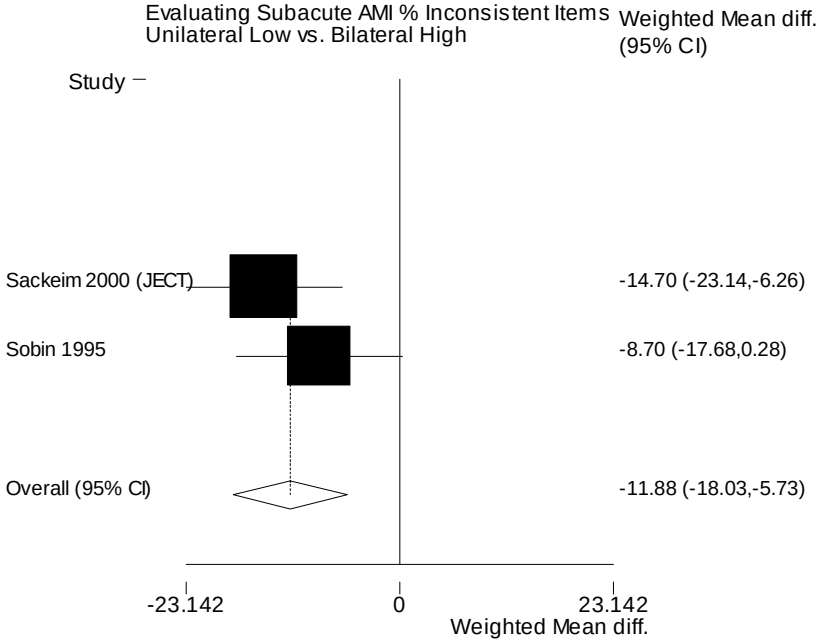

**Figure 22. AMI Sub-Acute (1 Day – 1 Week): Unilateral Low vs. Unilateral Medium**

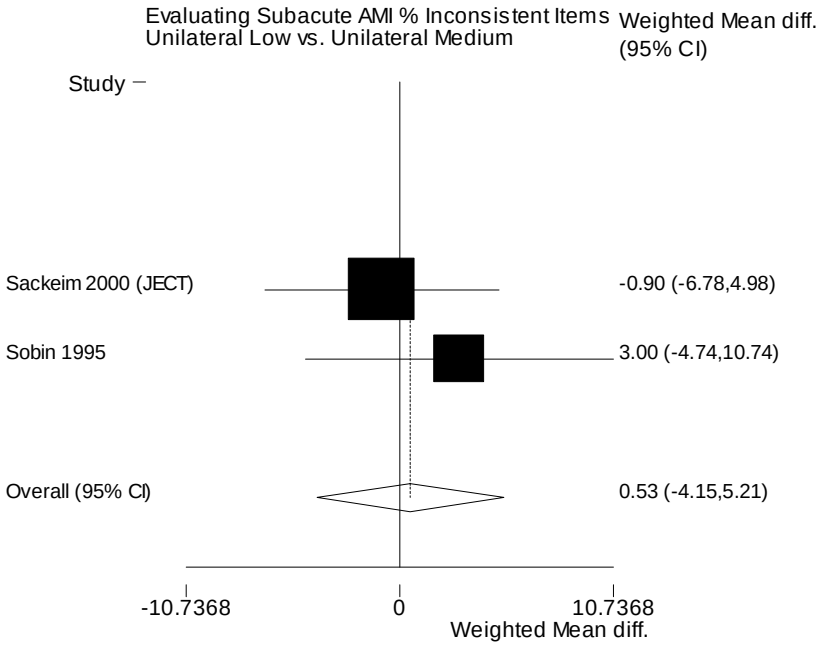


**Figure 23. AMI Sub-Acute (1 Day – 1 Week): Bilateral Low vs. Bilateral High**

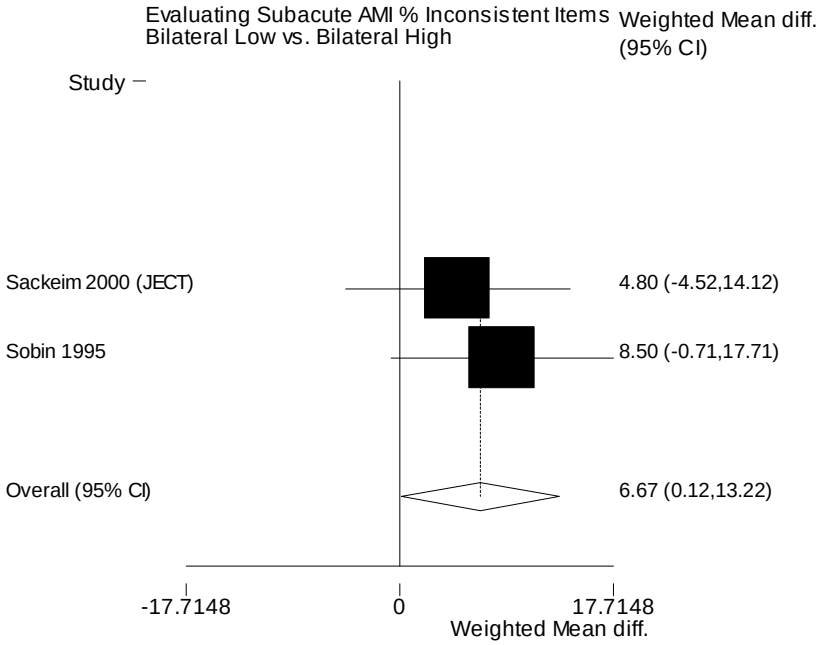

**Figure 24. Depression ECT vs. Sham**

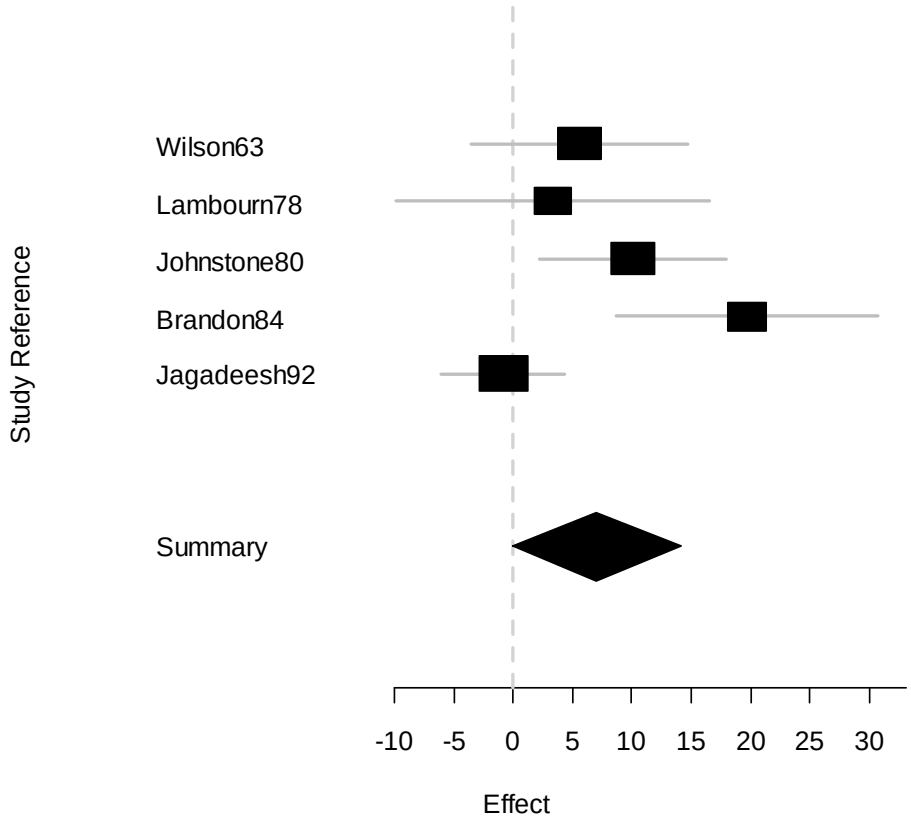


Figure 24 shows overall estimate and all study specific estimates

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

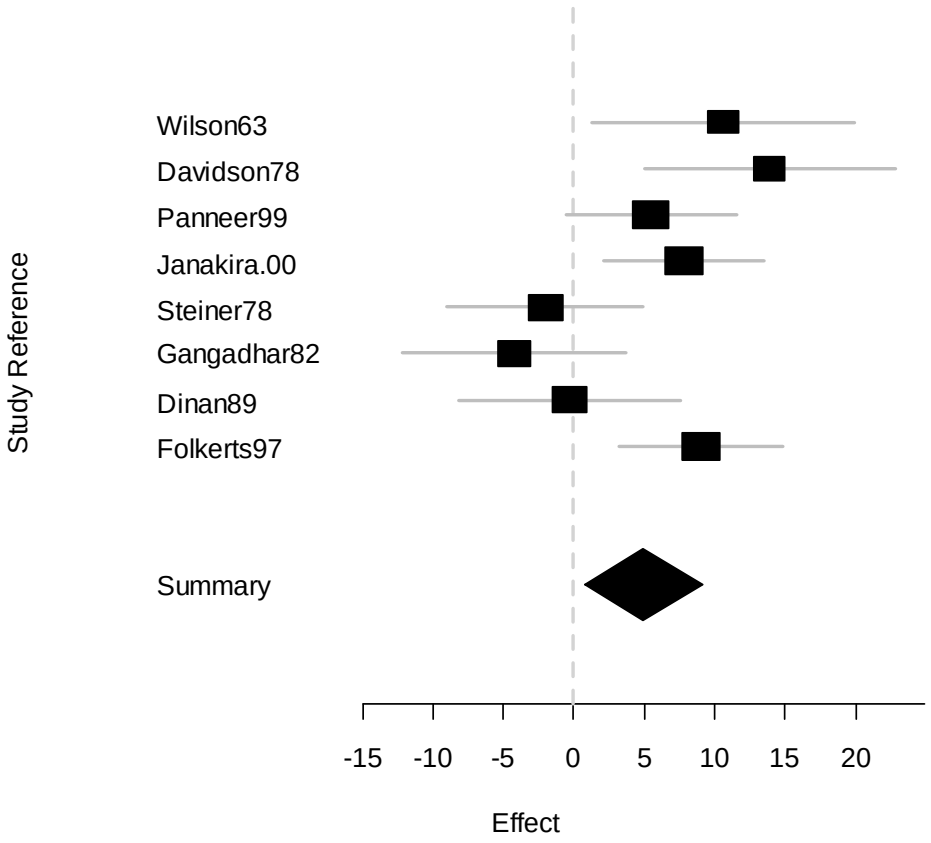


Figure 25 shows overall estimate and all study-specific estimates

**Figure 26. Schizophrenia: ECT vs. Sham**

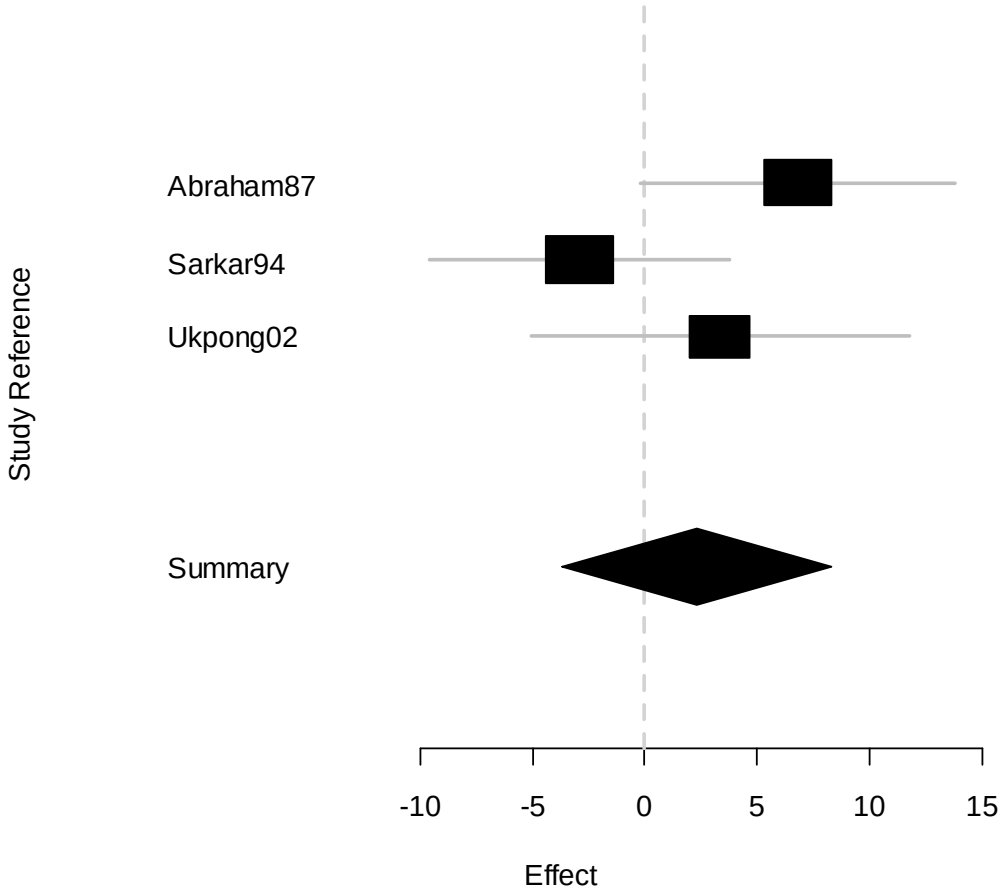


Figure 26 shows overall estimate and all study-specific estimates

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

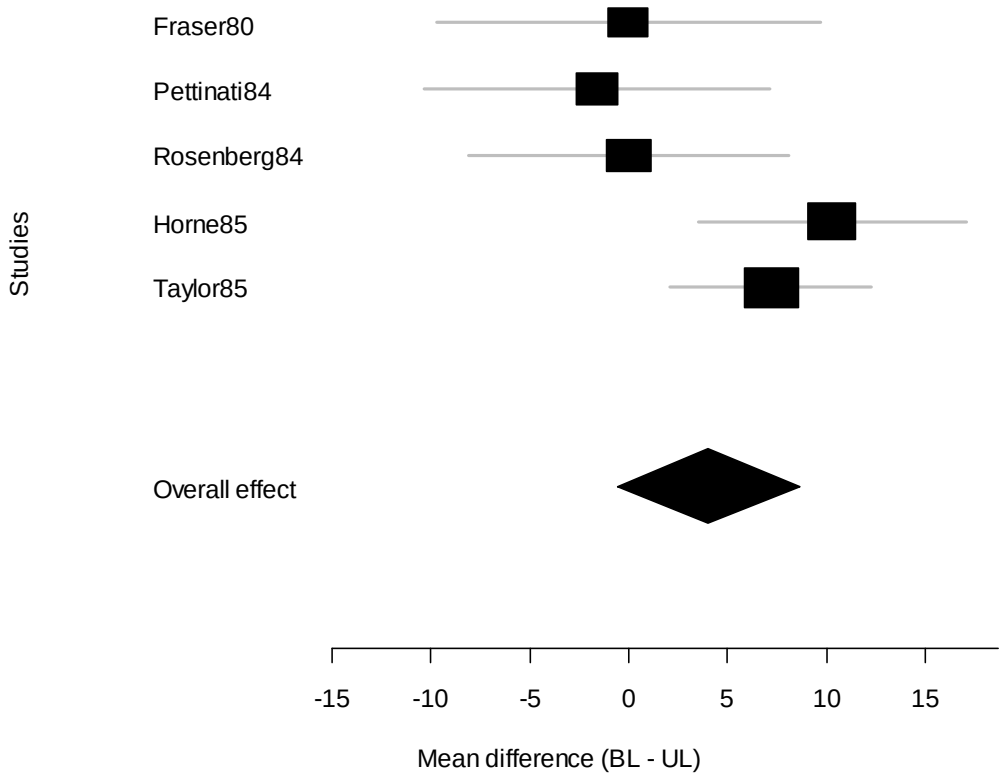


Figure 27 shows overall estimate and all study-specific estimates.

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

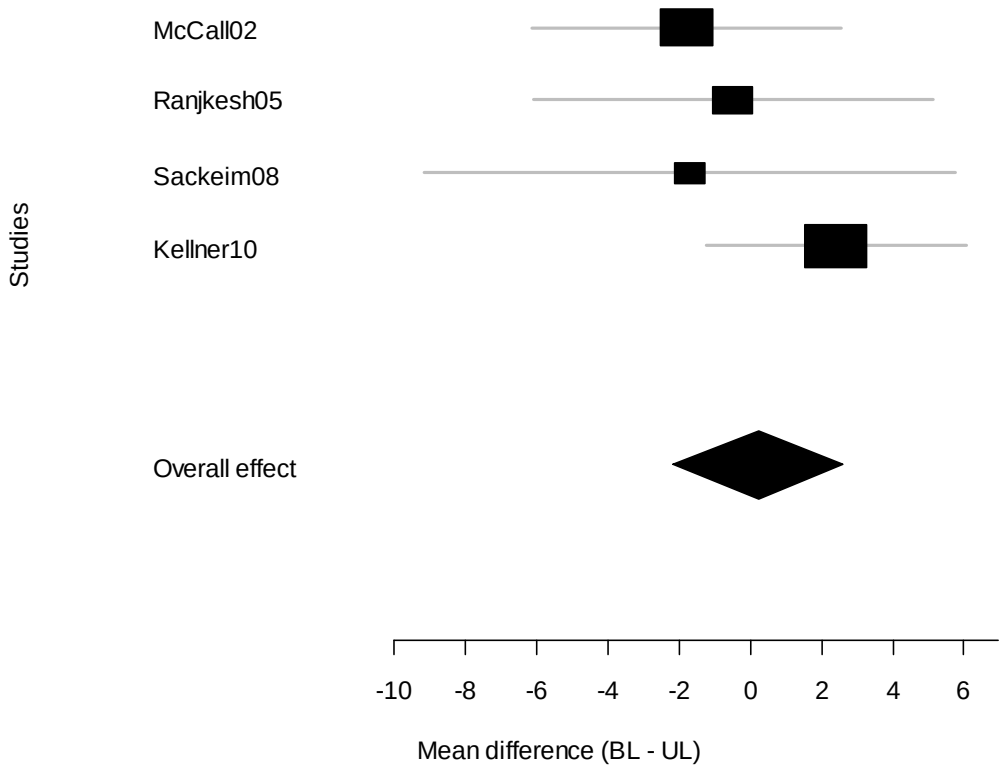


Figure 28 shows overall estimate and all study-specific estimates.

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

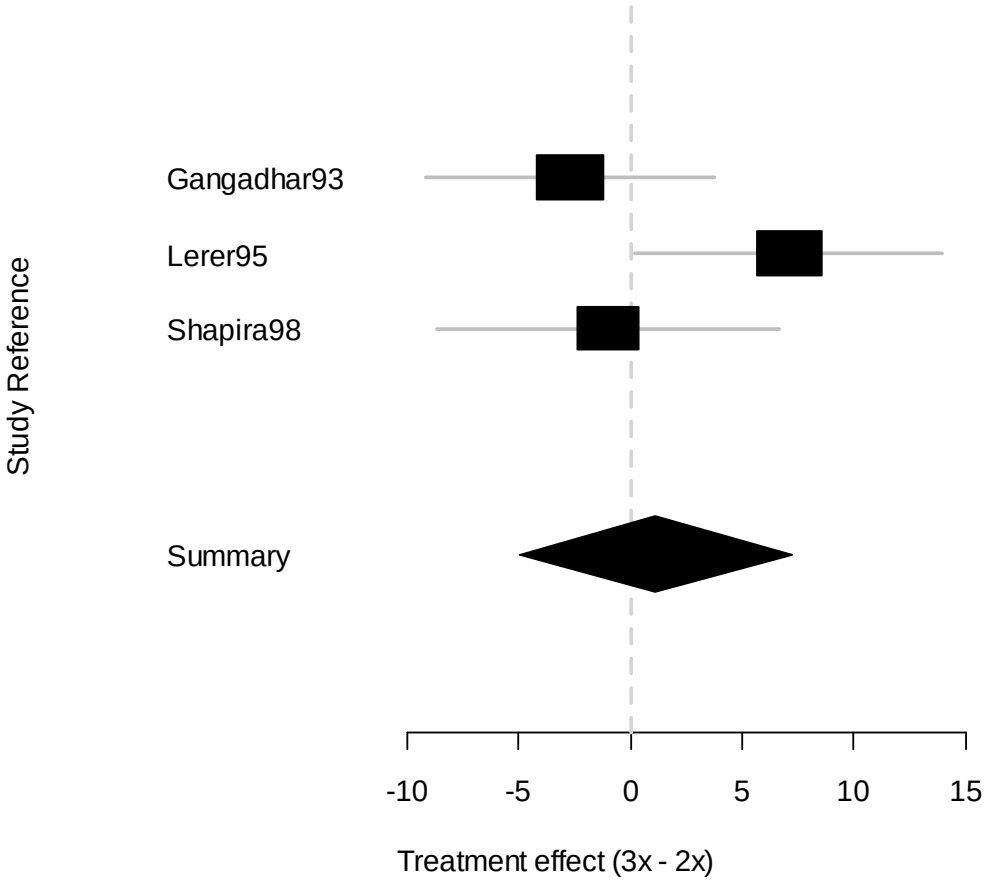


Figure 29 shows overall estimate and all study-specific estimates.

**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)<br>2. ECT BL (24)<br>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)<br>2. Anesthesia/placebo (4)<br>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)<br>2. IMI(20)<br>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)<br>2. ECT/placebo (6)<br>3. Sham/IMI (6)<br>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)<br>2. ATI (10)<br>3. placebo(4)<br>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<br>2. Sham | 1 D<br>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<br>2. Sham | 1 W<br>1 M<br>6 M | HRSD | SS: Real better than sham post-course (weekly assessment)<br>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)<br>2. Sham (11) | 5 D | BDI<br>Clinical assessments<br>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)<br>2. Sham (42) | Mid course (2 w)<br>Post course<br>8 W<br>24 W | HRSD | SS: 2 W (mid course) and post course<br>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<br>2. ECT RUL<br>3. Sham | Post<br>1 M<br>3 M<br>6 M | MADRS, HRSD | SS: ECT (BL and RUL) v sham post course.<br>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)<br>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)<br>2. Placebo(21)<br>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)<br>2. ECT/placebo (6)<br>3. Sham/IMI (6)<br>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)<br>2. IMI (73)<br>3. Phenelzine (38)<br>4. Marplan (68)<br>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)<br>2. Placebo (61)<br>3. IMI (63)<br>4. Phenelzine (61) | 4 W after initiation of treatment, 6 M | Clinical assessment | SS: 4w ECT and IMI better than placebo<br>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)<br>2. ATI (10)<br>3. placebo(4)<br>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)<br>2. antidepressant (10)<br>3. placebo (12)<br>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)<br>2. IMI (19) | 1 M after initiation of trial | Clinical assessment | NSS | Categorical analysis |
| **Harris** | 1960 | 12 | Depressive reaction | 1. ECT/placebo (4)<br>2. Sham/placebo (4)<br>3. Sham/phenelzine (4) | 2 W after initiation of trial | Clinical assessment | NST | All women subjects |
| **Robin** | 1962 | 26 | Depression | 1. ECT/placebo (14)<br>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<br>2. IMI<br>3.Tranylcypromine/trifluoperazine<br>4.ATI<br>5. Pheniparzine<br>6. Phenelzine<br>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)<br>2. ECT/placebo (6)<br>3. Sham/imi (6)<br>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)<br>2. Placebo (61)<br>3. IMI (63)<br>4. Phenelzine (61) | 4 W<br>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)<br>2. ATI (10)<br>3. placebo(4)<br>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)<br>2. IMI (16)<br>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)<br>2. Placebo(21)<br>3. IMI (21) | Post treatment | WPRS, MMPI psychasthenia, depression, Clyde mood scale | SS: IMI better than ECT.<br>NSS: ECT not better than IMI or placebo | No SD. All women subjects. |
| **Greenblatt** | 1964 | 281 | Depression mixed dx, none >50% | 1. ECT (63)<br>2. IMI (73)<br>3. Phenelzine (38)<br>4. Marplan (68)<br>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)<br>2. ATI/phenelzine (8) | Post treatment | HRSD, BDI, STAI | NST | |
| **Steiner** | 1978 | 12 | Depression | 1. ECT (4)<br>2. IMI/placebo (4)<br>3. IMI/T3 (4) | Post (5 W p initiation) | HRSD, CGI | Continous<br>Dichotomous<br>NSS. | All women subjects.<br>Individual HRSD data. |
| **Gangadhar** | 1982 | 32 | Endogenous depression | 1. ECT/placebo (11)<br>2. IMI/sham (13) | 4, 6, 8, 12, 24 W | HRSD | NSS all comparisons. | ECT 4 wk trial + mECT.<br>Both groups maintained improvement to 24 M. |
| **Dinan** | 1989 | 30 | Major depression-tricyclic nonresponders | 1. TCA/ECT<br>2. TCA/lithium | 3 W | HRSD | NSS | Both groups improved.<br>Lithium responded more rapidly with more mental state , changed by 7 D. |
| **Folkerts** | 1997 | 39 | Major depression ATHF ≥2 | 1. ECT<br>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)<br>2. IMI (14) | 4 W | HRSD17, MADRS, BDI, VAS, CGI | NSS: between groups.<br>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)<br>2. IMI (15)<br>3. yoga (15) | 4 W | BDI, HRSD | SS: ECT better than yoga.<br>NSS: Yoga and IMI.<br>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)<br>2. antidepressant (10)<br>3. placebo (12)<br>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)<br>2. IMI (37)<br>3. Phenelzine (30)<br>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<br>BL | 1 D<br>3 W | HRSD | NSS: UL = BL at either time point | |
| Weiner | 1986 | 53 | MDD, RDC | Pulse UL<br>Sine UL<br>Pulse BL<br>Sine BL | 6 M | HRSD<br>Zung self rating depression scale | NSS: all groups<br>SS: baseline change in ECT groups | 21 controls who received no ECT |
| Janicak | 1991 | 27 | Depressed | ULND<br>BL | 3-5 D<br>6 M | HRSD24 | NSS: between groups<br>SS: improvement from baseline at both time points | |
| Sackeim | 2000 | 80 | MDD, RDC | RUL 1.5ST<br>RUL 2.5ST<br>RUL 6ST<br>BL 2.5ST | 1-2 D<br>1 W | HRSD<br>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<br>RUL 6ST UBP<br>BL 2.5ST BP<br>BL 2.5ST UBP | 2 D<br>1 W | HRSD<br>BDI, CGI | SS: UBP BL worse than other 3 groups. | Ungraph |
| McCall | 2000 | 72 | MDE DSM IIIR | RUL 2.25ST<br>RUL fixed hi | 1-2 D | HRSD21 | SS: high dose RUL better than moderate dose<br>NST: change from baseline | |
| Heikman | 2002 | 24 | MDE | RUL 5ST<br>RUL 2.5 ST<br>BF ST | 1-3 D | HRSD 17 | SS: high dose RUL faster response than low dose BF.<br>NSS: trend toward higher response with high dose RUL | |
| McCall | 2002 | 77 | MDE | RUL 8ST (40)<br>BL 1.5ST (37) | 1-3 D<br>2 W<br>4 W | HRSD21<br>BDI | NSS: RUL 8ST not different then BL1.5 ST<br>NST: but appears to be some improvement from baseline, then relapse | |
| Eschweiler | 2007 | 92 | Pharmacoresistant major depression | BF<br>RUL | 1 D | HRSD21 | NSS: between groups difference | |
| Kimball | 2009 | 66 | MDE, DSMIIIR | Moderate titrated RUL<br>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<br>BT 1.5 ST (72)<br>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)<br>RUL (22) | 48-73 H | HRSD15 | Both demonstrate significant clinical improvement. SS: BL better | |
| Levy | 1968 | 40 | Depression | UL<br>BL | 6 H | Cronholm Ottosson | NSS trend for BL | 35 J for all treatments |
| Zinkin | 1968 | 102 | Depressive illness | BL (50)<br>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)<br>ULD (10)<br>ULND (10) | 28-31 H | BDI<br>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<br>ULD<br>ULND | 3 D<br>4 W | BDI | NSS: between groups<br>SS: all groups change from baseline | |
| Rosenberg | 1984 | 35 | Major affective or schizoaffective disorder (DSMIII) | BL<br>UL | 1W | HRSD | NSS: between groups difference<br>SS: all groups change from basleine. | |
| Gregory | 1985 | 69 | Depressive illness | BL<br>UL<br>sham | <2 D<br>1 M<br>3 M<br>6 M | HRSD<br>MADRS, PIRS | SS: UL and BL significantly improved compared to sham<br>NSS: UL and BL | |
| Horne | 1984 | 48 | MDD RDC | BL placebo (12)<br>BL Dexameth (12)<br>UL placebo (12)<br>UL Dexameth (12) | <1 D | HRSD<br>BPRS<br>BDI | NSS: between groups<br>SS: change from baseline | Combined across placebo and dexamethasone groups. Dexamethasone may impede recovery of depression |
| Ranjkesh | 2005 | 45 | MDD | BF 1.5ST<br>BT ST<br>RUL 5ST | 1 D | HRSD24 | NSS: all groups | BF moderate dose has same effectiveness as RUL or BL. |
| Pettinati | 1984 | 28 | 28<br>15<br>13 | BL (15)<br>RUL (13) | 1 W | HRSD<br>BDI | B: pre 21.6 (7.9), post 11.5 (7.9)<br>U: pre 21 (10), post 9.3 (7.2) | Right handed |
| Stoppe | 2006 | 39 | MDD, geriatric | RUL >5ST (17)<br>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)<br>3x per week (15) | 24-48 H<br>6 M | HRSD<br>CGI | NSS: no between groups difference<br>SS: improvement from baseline | 2x per week group received 1 sham per week<br>ECT: BL treatment |
| Lerer | 1995 | 52 | MDD, endogenous | 2x per week (23)<br>3x per week (24) | 1 W<br>1 M | HRSD | NSS: no between groups difference<br>SS: improvement from baseline | |
| Shapira | 1998 | 31 | Major Depression, endogenous subtype | 2x per week (14)<br>3x per week (17) | 1 D | HRSD | NSS: between groups continuous analysis<br>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.<br>2x per week group received 1 sham per week |
| Janakiramaiah | 1998 | 40 | MDD with melancholia (DSM-IIIR) | 1x per week high dose<br>1x per week low dose<br>3x per week High dose<br>3x per week Low dose | 48 H<br>1M | HRSD | SS: at 48 H, improvement from baseline all groups<br>SS: at 48 H, 3x per week more improvement than 1x per week | |
| McAllister | 1987 | 20 | MDE (DSM-III) | 2x per week<br>3x per week | 2 W, 4 W after initiation of trial | HRSD<br>BDI | NSS: no between groups difference<br>SS: improvement from baseline at 4 W | ECT UL treatment |
| Segman | 1995 | 47 | MDE, endogenous subtype (RDC) | 2x per week (23)<br>3x per week (24) | 1 W | HRSD | NSS: no between groups difference, trend favoring 3x per week. | Responder analysis |

Abbreviations:
ATI: amitriptyline

BDI: Beck Depression Inventory
BL: bilateral
BT: bitemporal
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
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 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)<br>2. Nonconvulsive ECT x 4W (10)<br>3. Pentothal x 4W (10) | 3 W<br>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)<br>Insulin coma (x 30) (15)<br>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<br>2. ECT succinylcholine<br>3. ECT thiopental<br>4. thiopental<br>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.<br>Schizoaffective group responded more than depression group. |
| **Doongaji** | 1973 | 86 | Schizophrenia | 1. ECT ULD (18)<br>2. ECT ULND (17)<br>3.ECT BL (19) | 1 D | BPRS | NSS: all groups | |
| **Taylor** | 1980 | 20 | Paranoid Schizophrenia | 1. ECT (10)<br>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<br>2. ECT and placebo | 7 D<br>20 D | BPRS, CGI | SS: between groups 7 D<br>NSS: 20 D<br>SS: baseline change both groups | |
| **Brandon** | 1985 | 19 | Schizophrenia | CPZ and,<br>1. ECT (9)<br>2. Sham (8) | 4 W<br>12 W<br>28 W after initiation of trial | MASS | Continuous<br>SS: between groups at 4 W<br>NSS: 12, 28 W | 8ECT treatments. Also on CPZ. |
| **Abraham** | 1987 | 22 | Schizophrenia | Trifluoperazine and,<br>1. ECT x 8 (11)<br>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.<br>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,<br>1. ECT BL sine<br>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,<br>1. BL ECT 1 ST (21)<br>2. BL ECT 2 ST (21)<br>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,<br>1. ECT (9)<br>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
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

**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)<br>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<br>2. ECT RUL<br>3. ECT LUL<br>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)<br>2. ECT BT low energy(14) | After 6 ECT and post-treatment | YMRS<br>HRSD | NSS: After 6 and final, YMRS no difference, BF mod less MMSE decline | |
| **Hiremani** | 2008 | 36 | Mania | 1. ECT BF (17)<br>2. ECT BT(19) | 21 D | YMRS | SS: BF quicker decline than BT | |
| **Mohan** | 2009 | 50 | Mania | ECT BL ST (26)<br>ECT BL 2.5ST (24) | Post treatment | YMRS, CGI, MMSE, WMS, autobio mem scale | Dichot: CGI data.<br>Cont: YMRS unusable. Cognitive data usable.<br>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)<br>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<br>BL | 1 D<br>3 W | HRSD | NSS: UL = BL at either time point | |
| Weiner | 1986 | 53 | MDD, RDC | Pulse UL<br>Sine UL<br>Pulse BL<br>Sine BL | 6 M | HRSD<br>Zung self rating depression scale | NSS: all groups<br>SS: baseline change in ECT groups | 21 controls who received no ECT |
| Janicak | 1991 | 27 | Depressed | ULND<br>BL | 3-5 D<br>6 M | HRSD24 | NSS: between groups<br>SS: improvement from baseline at both time points | |
| Sackeim | 2000 | 80 | MDD, RDC | RUL 1.5ST<br>RUL 2.5ST<br>RUL 6ST<br>BL 2.5ST | 1-2 D<br>1 W | HRSD<br>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<br>RUL 6ST UBP<br>BL 2.5ST BP<br>BL 2.5ST UBP | 2 D<br>1 W | HRSD<br>BDI, CGI | SS: UBP BL worse than other 3 groups. | Ungraph |
| McCall | 2000 | 72 | MDE DSM IIIR | RUL 2.25ST<br>RUL fixed hi | 1-2 D | HRSD21 | SS: high dose RUL better than moderate dose<br>NST: change from baseline | |
| Heikman | 2002 | 24 | MDE | RUL 5ST<br>RUL 2.5 ST<br>BF ST | 1-3 D | HRSD 17 | SS: high dose RUL faster response than low dose BF.<br>NSS: trend toward higher response with high dose RUL | |
| McCall | 2002 | 77 | MDE | RUL 8ST (40)<br>BL 1.5ST (37) | 1-3 D<br>2 W<br>4 W | HRSD21<br>BDI | NSS: RUL 8ST not different then BL1.5 ST<br>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<br>RUL | 1 D | HRSD21 | NSS: between groups difference | |
| Kimball | 2009 | 66 | MDE, DSMIIIR | Moderate titrated RUL<br>Fixed high dose RUL | 1-2 D | HRSD21 | NSS: between groups difference | |
| Kellner | 2010 | 230 | Bipolar and unipolar depression | BF 1.5ST<br>BT 1.5 ST (72)<br>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)<br>RUL (22) | 48-73 H | HRSD15 | Both demonstrate significant clinical improvement. SS: BL better | |
| Levy | 1968 | 40 | Depression | UL<br>BL | 6 H | Cronholm Ottosson | NSS trend for BL | 35 J for all treatments |
| Zinkin | 1968 | 102 | Depressive illness | BL (50)<br>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)<br>ULD (10)<br>ULND (10) | 28-31 H | BDI<br>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<br>ULD<br>ULND | 3 D<br>4 W | BDI | NSS: between groups<br>SS: all groups change from baseline | |
| Rosenberg | 1984 | 35 | Major affective or schizoaffective disorder (DSMIII) | BL<br>UL | 1W | HRSD | NSS: between groups difference<br>SS: all groups change from basleine. | |

| First Author | Year | N | Subjects | Comparison | Time point | Efficacy Measures | Outcome | Comment |
|---|---|---|---|---|---|---|---|---|
| Gregory | 1985 | 69 | Depressive illness | BL<br>UL<br>sham | <2 D<br>1 M<br>3 M<br>6 M | HRSD<br>MADRS,<br>PIRS | SS: UL and BL significantly improved compared to sham<br>NSS: UL and BL | |
| Horne | 1984 | 48 | MDD RDC | BL placebo (12)<br>BL Dexameth (12)<br>UL placebo (12)<br>UL Dexameth (12) | <1 D | HRSD<br>BPRS<br>BDI | NSS: between groups<br>SS: change from baseline | Combined across placebo and dexamethasone groups. Dexamethasone may impede recovery of depression |
| Ranjkesh | 2005 | 45 | MDD | BF 1.5ST<br>BT ST<br>RUL 5ST | 1 D | HRSD24 | NSS: all groups | BF moderate dose has same effectiveness as RUL or BL. |
| Pettinati | 1984 | 28 | 28<br>15<br>13 | BL (15)<br>RUL (13) | 1 W | HRSD<br>BDI | B: pre 21.6 (7.9), post 11.5 (7.9)<br>U: pre 21 (10), post 9.3 (7.2) | Right handed |
| Stoppe | 2006 | 39 | MDD, geriatric | RUL >5ST (17)<br>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)<br>•Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)<br>•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)<br>•Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)<br>•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<br>•Use of ultrabrief pulse (0.3 msec) stimulus<br>•Exclusive use of unilateral nondominant electrode placement<br>•Use of bifrontal electrode placement<br>•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<br>•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<br>• Adherence to software<br>• Development standards<br>• Adherence to mechanical design standards<br>• Bench testing (to characterize device output) | Standards, testing |

| Risk/Adverse Event | Types | Risk Characterized | Proposed Mitigation Factors | Regulatory Mechanism |
|---|---|---|---|---|
| | | | • Electrical safety testing<br>• 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<br>•Use of ultrabrief pulse (0.3 msec) stimulus<br>•Exclusive use of unilateral nondominant electrode placement<br>•Use of bifrontal electrode placement<br>•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)<br>•Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation)<br>•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)<br>•Appropriate procedure monitoring (including EKG, blood pressure, pulse, respiratory rate and oxygen saturation<br>•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. <u>Depression: ECT vs. Sham</u>

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 37

*The Journal of ECT*
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Editorial

# Memory and ECT: From Polarization to Reconciliation

Discussions of the cognitive effects of electroconvulsive therapy (ECT) have been polarized for decades. Critics of the treatment often claim that patients only seem improved after ECT because they are "punch drunk"—too confused to maintain a depressed state (Sterling, 2000). Others contend that profound and permanent amnesia is common and a clear sign that the treatment causes brain damage (Frank, 1990). Still others have charged that the adverse effects are more pervasive than retrograde amnesia, with ECT impairing the most complex of human cognitive functions, i.e., intelligence, creativity, judgment, foresight, etc. (Breeding, 2000).

In contrast, practitioners and researchers often state that the adverse cognitive effects of ECT are transient. Within a few weeks of the acute treatment course, cognitive function is restored. If any residual deficit is acknowledged, it is restricted to gaps in memory for events that occurred close in time to the treatment. Some state that the memory loss is limited to the period of the treatment, while others extend this to a period of a few weeks or months surrounding the ECT course. Complaints of pervasive and persistent memory loss have often been attributed to causes other than ECT, typically persistent psychiatric disability.

Both views are out of keeping with clinical experience and research. Scores of studies have failed to find an association between clinical outcome and the depth of any cognitive deficit during or following ECT (Sackeim, 1992). People do not get better because they are confused or amnestic. To the contrary, many cognitive domains, including "intelligence," improve shortly following ECT (Sackeim et al., 1992). On the other hand, virtually all patients experience some degree of persistent and, likely, permanent retrograde amnesia. A series of recent studies demonstrates that retrograde amnesia is persistent, and that this long-term memory loss is substantially greater with bilateral than right unilateral ECT (Weiner et al., 1986b; McElhiney et al., 1995; Lisanby et al. [in press]; Sackeim et al. [in press]. It has also become clear that for rare patients the retrograde amnesia due to ECT can be profound, with the memory loss extending back years prior to receipt of the treatment.

As a field, we have more readily acknowledged the possibility of death due to ECT than the possibility of profound memory loss, despite the fact that adverse effects on cognition are by far ECT's most common side effects. Individual differences and hypersensitivity to side effects characterize virtually all medical procedures and pharmacological treatments. That ECT would have an especially narrow range of amnestic effects would be a remarkable exception.

Undoubtedly, reaching consensus on this fundamental issue has been impeded by the fact that memory complaints are subjective and can have multiple determinants. Some of the neuropsychological deterioration seen after ECT is due to natural progression of an

underlying illness. In young patients, seemingly irreversible cognitive decline may accompany the first manifestation of a psychotic disorder (Wyatt, 1991). When ECT is used early in the treatment of such patients, the precipitous cognitive decline is at times wrongly attributed to this therapeutic intervention. Similarly, ECT may unmask an underlying dementia in older patients.

It is also the case that in all populations studied (normal, neurological, psychiatric), current mood state is the most important correlate of subjective evaluation of memory function (Coleman et al., 1996). We believe that our memory (and other cognitive functions) are less intact when we are depressed. On the other hand, regardless of the population studied, subjective evaluations and objective measures typically show poor association (Sackeim and Stern, 1997).

Another complication is that some patients with persistent memory complaints following ECT have no treatment-related deficits. Rather, the subjective experience of cognitive deficit is related to ongoing psychopathology. While there is compelling evidence that this occurs with some frequency (Freeman et al., 1980), for understandable reasons the profession has not emphasized this phenomenon. In the consent form recommended by the 1990 APA Task Force Report on ECT (American Psychiatric Association, 1990), it was acknowledged that a minority of patients report severe memory problems, with the comment that, "The reasons for these rare reports of long-lasting impairment are not fully understood" [p. 158]. Some of the reasons were understood, but it is uncomfortable for the field to be perceived as "blaming the victim," and attributing memory complaints to unresolved psychiatric disturbance, even if true.

However, aside from each of these possibilities, some patients experience profound memory loss due to ECT. Most ECT practitioners have encountered fully credible patients who are distressed by the magnitude of their persistent post-ECT amnesia. Skeptics will argue that complaints of memory loss do not necessitate true disability, and that we have no objective "dipstick" to verify that memory is truly impaired. On the other hand, there is no dearth of patients who have received ECT who believe that the treatment was valuable, often life saving, who are not litigious, who return to productive activities, and yet report that a large segment of their life is lost. These patients often report a classic temporal gradient in their retrograde amnesia, with the memory loss most accentuated for the time period (months to years) closest in time to the treatment, with sparing of more remote memories. It is hard to imagine that such reports of a classic retrograde amnestic syndrome, with sparing of other cognitive functions, are simply fabricated. Attributing these subjective deficits to ongoing psychopathology or natural disease progression would seem disingenuous and defensive.

There have been few personal accounts of the amnesia following ECT (Wolfe, 1969). In this issue of *The Journal of ECT*, Anne B. Donahue provides a compelling description of the nature and impact of the persistent memory loss she experiences. In many ways this is a courageous statement, acknowledging the clinical benefit of the treatment, and alerting the field about the mismatch between our efforts to assess objectively cognitive alterations and the phenomenology of the memory loss. Donahue's paper also underscores the public relations fallout and, more critically, the turmoil to individuals that result when former patients experience chronic and pervasive memory loss and yet the field denies the possibility of its occurrence.

Fortunately, the tide has turned. The field has greater awareness of the common am-

nestic effects of the treatment, and reconciliation is occurring with the experience of exceptional patients with substantial and sustained memory loss. The newly revised APA Task Force Report (APA, in press) on ECT states:

In many patients the recovery from retrograde amnesia will be incomplete, and there is evidence that ECT can result in persistent or permanent memory loss. Owing to a combination of anterograde and retrograde effects, many patients may manifest persistent loss of memory for some events that transpired in the interval starting several months before and extending to several weeks following the ECT course. There are individual differences, however, and, uncommonly, some patients may experience persistent amnesia extending several years prior to ECT. Profound and persistent retrograde amnesia may be more likely in patients with preexisting neurological impairment and patients who receive large numbers of treatments, using methods that accentuate acute cognitive side effects (e.g., sine wave stimulation, bilateral electrode placement, high electrical stimulus intensity).

This change in attitude and understanding compel closer clinical and research attention to the cognitive effects of treatment. The papers in this special issue highlight some of the key unanswered questions.

## TREATMENT TECHNIQUE AND AMNESIA

It has become increasingly clear that the sophistication with which ECT is conducted impacts not only on short-term cognitive effects, but also on the likelihood of long-term persistent changes. Lerer and colleagues review the effects of treatment schedule (using bilateral ECT) on adverse cognitive effects. This work (Lerer et al., 1995; Shapira et al., 1998) has demonstrated a principle regularly used by clinicians. Increasing the interval between treatments reduces the magnitude of cognitive impairment. In terms of long-term consequences, the choice of electrode placement (right unilateral versus bilateral ECT) may be more consequential than the electrical dosage administered and perhaps the treatment schedule (Weiner et al., 1986b; Sackeim et al., 1993; McElhiney et al., 1995; Lisanby et al., in press; Sackeim et al., in press). It appears that high dosage right unilateral ECT is as effective as robust forms of bilateral ECT, but has significantly less probability of resulting in marked and persistent retrograde amnesia (Abrams et al., 1991; Sackeim et al., in press; McCall et al., in press). Further refinements of ECT technique may additionally limit cognitive side effects. Perhaps the most attractive possibility is shortening the width of the brief-pulse stimulus. The pulse widths most commonly used are an order of magnitude longer than that needed for neuronal depolarization, and thus necessarily involve stimulation after neurons have fired (Sackeim et al., 1994).

Some practitioners have held the view that the focus of ECT research in the last two decades on optimizing stimulus dosing and waveform, electrode placement, and spacing of treatments was largely academic. High intensity treatment (e.g., high fixed dosage bilateral ECT) is the least complicated to administer and has the highest probability of efficacy. Given the view that all adverse cognitive effects are transient, with rapid resolution, for some there was little incentive to adopt new treatment methods. As recent research has consistently demonstrated that treatment technique impacts on the magnitude of persistent memory loss, this position becomes difficult to defend.

## INDIVIDUAL DIFFERENCES AND ADVERSE COGNITIVE EFFECTS

It would be comforting to attribute all the negative cognitive outcomes with ECT to poor technique. However, regardless of how ECT is performed there are individual differences. Using the same technique, clinicians regularly encounter patients who respond to ECT without any cognitive alterations (or, indeed, may show resolution of preexisting cognitive deficits during and following the ECT course) as opposed to patients who develop delirium. Why?

Over the 65 years of use of convulsive therapy, there have been scores of studies examining the patient characteristics (phenomenology, clinical history, treatment history, biology) that predict therapeutic outcome (Scott, 1989; Nobler and Sackeim, 1996). Essentially, there has been one systematic report on the patient characteristics that predict short- and long-term cognitive outcome after ECT (Sobin et al., 1995). That study suggested that patients with pre-ECT global cognitive impairment and those with prolonged disorientation in the postictal state have more profound short- and long-term retrograde amnesia. This would suggest that treatment techniques be "softened" especially for patients with these characteristics. However, practitioners routinely face issues of this type that are unexplored. Does preexisting neurological illness (stroke, Parkinson's disease, dementia, etc.) predispose to long-term cognitive deficits? What is the contribution, if any, of comorbid substance abuse, concurrent antidepressant or antipsychotic pharmacotherapy, cardiac illness (low cardiac output), benzodiazepine use, etc., to post-ECT cognitive deficits? We have no answers to these questions.

## PREVENTION AND TREATMENT OF COGNITIVE DEFICITS

The side effects of many pharmacological treatments are actively treated (e.g., anticholinergics for neuroleptic-induced extrapyramidal symptoms). Electroconvulsive shock (ECS) is the most common procedure used to induce amnesia in animals to screen pharmacological compounds for protective effects on memory. Our estimate is that between 50–100 compounds have shown benefit in ECS models (Krueger et al., 1992). For example, in this issue Andrade and colleagues review research on herbal preparations that ameliorate the cognitive effects of ECS in animal models (Joseph et al., 1994; Faruqi et al., 1995; Andrade et al., 1995; Vinekar et al., 1998), and discuss the strengths and weaknesses of animal models in generalizing to human ECT.

The interest of the pharmaceutical industry in using ECS as a screening method for identifying compounds with promemory effects is not to develop adjunctive medications for ECT. The ECT market is too small, and the predominant aim has been to develop medications for the treatment of dementing disorders (Krueger et al., 1992). Consequently, only a handful of studies have tested pharmacological adjuncts for protective effects in ECT (Stern et al., 1991; Prudic et al., 1999).

Concerted research in this area has the potential for making an important clinical contribution, as well as advancing our understanding of the neurobiology of ECT's amnestic effects. One example illustrates these possibilities. There is considerable interest in the notion that ECT results in altered glutamatergic transmission, particularly in prefrontal and medial temporal lobe structures (Morinobu et al., 1997; Pilc et al., 1998; Hiroi et al., 1998), and that this increased excitatory transmission contributes to amnestic effects

(Chamberlin and Tsai, 1998). Long-term potentiation (LTP) has been commonly viewed as a model of memory formation, and ECS results in long-term disruption of LTP in the dentate gyrus (Stewart et al., 1994; Stewart and Davies, 1996). The NMDA antagonist, ketamine, protects against this disruptive effect (Stewart and Reid, 1994), raising the possibility that use of ketamine as an anesthetic, as opposed to the standard short-acting barbiturates, or use of other glutamatergic antagonists may have a protective effect on cognition (Reid and Stewart, 1997).

## THE NATURE AND NEUROBIOLOGY OF ADVERSE COGNITIVE EFFECTS

There are additional goals for future research on the cognitive consequences of ECT. We need to 1) better characterize the nature of memory deficits (i.e., what is forgotten), 2) better characterize the neural systems implicated in these amnestic effects, particularly the role of prefrontal versus medial temporal lobe memory systems, and 3) determine the impact of ECT on neurocognitive functions other than memory (Calev et al., 1995).

It has been commonly thought that the memory deficits following ECT reflect medial temporal lobe dysfunction (Squire, 1981; 1986a;1986b; Sackeim, 1992). The most prominent deficits are anterograde amnesia (rapid forgetting of newly learned information) and a temporally graded retrograde amnesia. ECT patients do not show deficits in priming, skill acquisition, or other types of procedural (nondeclarative) memory (Cohen and Squire, 1980; Squire et al., 1984; Graf et al., 1984; Squire et al., 1985). The rapid forgetting rate (Squire, 1981), preserved metamemory ("feeling of knowing") (Shimamura and Squire, 1986), and other features (Squire, 1982) distinguish the amnesia following ECT from that due to diencephalic lesions or Korsakoff's syndrome. This pattern, largely restricted to episodic, declarative memory, suggests that the underlying disturbance is one of consolidation and/or retrieval (Squire and Alvarez, 1995). The reversibility of amnesia, with the recovery of memories over time, particularly implicates an impaired retrieval process. The established role of medial temporal lobe structures in memory processes (Shimamura and Squire, 1987; Nadel and Moscovitch, 1997), the low threshold for afterdischarge and seizure elicitation in the hippocampus (Ajmone Marsan, 1972; Bragin et al., 1997), and the disruption by ECS of hippocampal processes implicated in memory (e.g., LTP) (Reid and Stewart, 1997) support the view that medial temporal lobe dysfunction is key.

However, there is hardly any physiological evidence linking medial temporal lobe dysfunction to the memory deficits following ECT. In this issue, we report that the development of EEG (electroencephalographic) theta activity in left frontal and temporal sites is associated with greater retrograde amnesia for autobiographical information, partially supporting the medial temporal lobe hypothesis. In contrast, there is consistent evidence that ECT exerts its most profound physiological effects in prefrontal cortex, as assessed by reductions in cerebral blood flow (Rosenberg et al., 1988; Silfverskiöld and Risberg, 1989; Nobler et al., 1994) and metabolic rate (Volkow et al., 1988; Guze et al., 1991), and the induction of EEG slow-wave activity (Fink and Kahn, 1956; Weiner et al., 1986a; Sackeim et al., 1996). Thus, there is the paradox that the most prominent cognitive effects are linked to a different brain region than the most pronounced physiological effects. There is a compelling need to examine associations between the magnitude of

cognitive effects and regional alterations in functional brain activity (e.g., metabolic rate) and biochemical parameters.

It is noteworthy that the classic deficits associated with hippocampal damage are a profound anterograde amnesia and a less marked retrograde amnesia (Russell and Nathan, 1946; Milner, 1970; Damasio et al., 1985). In contrast, ECT results in a rapidly resolving anterograde amnesia and persistent retrograde amnesia (Squire, 1986a; Weiner et al., 1986b; Sackeim et al., in press). In addition, the retrograde amnesia following hippocampal damage is believed to be greater for autobiographical than public (impersonal) events (Nadel and Moscovitch, 1997). We have recently shown that the opposite is the case following ECT (Lisanby et al., in press). Both in the short and long term, patients who received ECT had denser amnesia for events in the world (public knowledge) than for events in their own lives. Frontal lobe damage can result in profound retrograde amnesia (Stuss and Benson, 1986; Kopelman, 1992; Moscovitch, 1994; Shimamura, 1994), in some comparisons as great as temporal lobe pathology (Kopelman et al., 1999), and presumably due to the disruption of retrieval processes. In amnesic patients (with brain damage), anterograde and retrograde memory loss are often weakly associated, and there is evidence that tests of frontal lobe function can covary with the magnitude of retrograde amnesia (Kopelman, 1991). Thus, a reasonable argument can be made that our traditional view that the (retrograde) amnestic effects of ECT result from functional disruption of medial temporal lobe structures is wrong, and the retrograde amnesia may, in fact, have an important frontal lobe involvement.

Resolving this issue, while of obvious importance to our understanding of the neurobiology of retrograde amnesia, is also of clinical significance. The development of alternative electrode placements, such as the bifrontal (Lawson et al., 1990; Letemendia et al., 1993; Bailine et al., 2000) and the asymmetric (Swartz, 1994) techniques, are predicated on the notion that avoidance of temporal lobe stimulation minimizes adverse cognitive effects, while frontal lobe stimulation preserves efficacy. If prefrontal changes subserve the retrograde amnesia these efforts may be largely in vain.

The prefrontal cortex is linked to a variety of "executive functions," including working memory (holding information online), logical reasoning and abstraction, set shifting, temporal organization of behavior, planning, memory for the context of events, and inhibition of competing, prepotent responses (Baddeley, 1986; Stuss and Benson, 1986; Goldman-Rakic, 1987; Diamond, 1990; Fuster, 1990). Tasks assessing prefrontal functions may load on different dimensions than tasks presumed sensitive to medial temporal lobe function (episodic, declarative memory), and there is some evidence that performance on prefrontal tasks predicts the adequacy of memory for the source or context of information (Glisky et al., 1995) and retrograde amnesia (Kopelman, 1991). Executive functions are fundamental to organizing one's life and controlling behavior, yet there has been little investigation of the impact of ECT on this domain (Jones et al., 1988).

## SUBJECTIVE EXPERIENCE OF COGNITIVE EFFECTS

In this issue, Prudic and colleagues summarize what is known about patients' own assessments of the effects of ECT on cognition. It appears that over time there has been a detectable shift. In older studies, largely using sine wave stimulation, a long-term detrimental impact was observed, especially with bilateral ECT (Squire et al., 1979;

Squire and Slater, 1983). Modern studies report that within a few days of ECT the vast majority of patients evaluate their memory as improved (Sackeim et al., 1993; Sackeim et al. (in press). This shift may be attributable to the advances in ECT technique (use of titration, brief pulse stimulation, etc.).

However, we should not be sanguine. ECT research has mainly relied on a single instrument to obtain self assessments of memory function, the Squire Subjective Memory Questionnaire (SSMQ) (Squire et al., 1979). The SSMQ is limited in the dimensions of metamemory that it examines, and is extraordinarily complex in its instructions. Patients are asked to rate their current functioning for discrete cognitive activities relative to their functioning before the onset of the index episode of depression. Perhaps not surprisingly, it has been shown that a substantial number of responses to the SSMQ are of doubtful validity. It is not infrequent for patients to state that their current cognitive function a few days after ECT is superior to that before the onset of the depressive episode, an unlikely phenomenon (Coleman et al., 1996). Broader-based assessment techniques are needed. It is especially surprising that direct and simple inquiries about whether ECT has had a positive or detrimental effect on memory have not been used in recent research. An older literature illustrated that such direct inquiries were effective in distinguishing ECT waveforms (Medlicott, 1948) and electrode placements (Cannicott, 1962; Fleminger et al., 1970).

Prospective patients, family members, and the public often want to know the frequency with which patients report substantial memory impairment following ECT. While we believe that such reports are infrequent, there is little objective evidence to support this judgment or to even broadly estimate base rates. Indeed, our estimates of the probability of death with ECT are based on a more secure empirical foundation (Abrams, 1997) than our estimates of marked subjective memory loss. This should be a readily resolvable issue, and calls for a large sample study in community settings.

In short, as the quality and sensitivity of neurocognitive research in ECT have improved, increasing evidence has accumulated that some degree of persistent memory loss is common. As the dialectical political battles of the 1960s and 1970s recede, there is greater acceptance and acknowledgment by the profession that ECT may infrequently result in extensive retrograde amnesia. At the clinical level, this shift in perspective highlights the need for practitioners to update what is communicated in the consent process and to monitor cognitive outcomes. This shift also presents many challenges for research, the most important of which is to further reduce or eliminate these adverse effects of ECT.

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# EXHIBIT 38

*The Journal of ECT*
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# Electroconvulsive Therapy and Memory Loss: A Personal Journey

Anne B. Donahue

*Northfield, Vermont, U.S.A.*

**Summary:** The cause for the significant gap between research and anecdotal evidence regarding the extent of some memory loss after electroconvulsive therapy (ECT) has never been adequately explained. A patient's development of awareness and self-education about her severe side effects from ECT raises questions regarding many current assumptions about memory loss. ECT-specific studies, which conclude that side effects are short term and narrow in scope, have serious limitations, including the fact that they do not take into account broader scientific knowledge about memory function. Because of the potential for devastating and permanent memory loss with ECT, informed consent needs significant enhancement until advancing research on both improved techniques and on better predictive knowledge regarding memory loss progresses to making a greater impact on clinical applications. Follow-up care and education in coping skills need to be a regular part of ECT practice when patients do experience severe effects.

**Key Words:** Electroconvulsive therapy—Memory loss.

## INTRODUCTION

Occasionally, I feel bitter. More often, it is a sadness, a sense of a deep loss that may not even have had to happen. It is a grief that keeps deepening over time, because there is hardly a week that goes by that I do not discover yet another part of my life that is lost somewhere in my memory cells.

Despite that, I remain unflagging in my belief that the electroconvulsive therapy I received in the fall of 1995 and then the spring of 1996—33 treatments, initially unilateral and then bilateral—may have saved not just my mental health, but my life. If I had the same decision to make over again, I would choose ECT over a life condemned to psychic agony, and possible suicide. Like a heart patient who has to choose the risks of surgery over the risks of heart attack or stroke; like the cancer victim who must choose the horrible side effects of chemotherapy over certain death to the disease—I live with and accept the price I paid to break the stranglehold of a seemingly intractable and severe depression.

Received February 22, 1999; accepted January 11, 2000.
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I was not particularly anxious about my memory loss. I "knew" from my doctors that my memory would mostly recover within 6 months, so I was very casual, almost flippant, about the side effects. Throughout that fall, my mood was fairly positive, and since it was a temporary effect, it was something to make fun of among friends: jokes from them, "You mean you don't remember that $500 I loaned you?" or my mock insistence that it was their memory that was impaired, not mine, "I know for a *fact* that we've never been to this restaurant before."

Perhaps more important to my light attitude was the fact that I had no concept of how much information was gone from my past. It may seem obvious, yet it becomes a truism that may cast one bit of light on those impairments that are not reported by patients when research follow-up is only done in the first few months: You cannot be aware of something that is missing. It is only through the gradual process of hearing others talk about the miscellany of life that one rebuilds the knowledge, though not necessarily the memory, of events past. Until that process develops, the vacuum remains unknown and unknowable, so the panic and sense of loss do not occur immediately. When, as in my case, follow-up assessment is not routinely done, the severe losses may remain unknown to the treating physicians, and any care for coping is thus left undeveloped.

It affected my relationships with newer, more casual friends in a very different way. I simply did not remember the status of our relationship. In addition, the gap in time caused by the gap in the corresponding memory period made it seem like far more time had passed than was real. I was not prepared to discuss ECT with them, and without being able to explain uncertain overtures, I was not comfortable approaching them. Most of these friends knew basically about my illness, and would have waited to hear from me, not wanting to intrude. The relationships with these people basically drifted away. Public stigma over mental health has been reduced somewhat in recent years, and it is not difficult for me to reveal my disability anymore, but ECT remains in a class of its own. I have encountered stunned silence or even horror.

As the 6-month marker came and went with only partial recovery of my recollection for past events, my focus began to change. I was again not doing as well emotionally, which affected my positive attitude. In addition, some mental health advocacy groups that were hosting a disability information day at the Vermont statehouse had asked me to put together a revised fact sheet on ECT. Feeling inadequately prepared, I did some superficial research.

I was completely stunned by the discrepancies I found. While multiple studies found any long-term amnesia to be extremely rare (as summarized by Sackeim (1992), informal accounts, advocacy group information, and newspaper exposés described extensive and broad-based risks (Breggin, 1979; Cauchon, 1995; Vermont Protection and Advocacy, 1996). Hearing claims such that ECT caused brain damage were terrifying to a layperson when discovered without yet knowing the questionable professional standing and credibility of the sources.

I had in fact experienced significant and long-term impairment that I could easily distinguish from ordinary memory fallibility. Yet as I reviewed what I had found, it seemed clear that comprehensive efforts to assess long-term adverse effects had not been made. I found repeated acknowledgment that more research was needed on memory loss (Culver et al., 1980; Weiner, 1984; Kaplan and Sadock, 1989; Calev, 1991; Sackeim, 1992; Devanand et al., 1994).

ECT series. But then I was told about all the fun we had sledding that weekend, the great airline fiasco one family endured, the serious hand injury a friend incurred on the rope swing—there are no pictures of these events, and it has become clear that the only memories I have are of those things that do exactly match the pictures. Are the memories completely suspect as false creations, or is a photo trigger more effective than a verbal trigger in bringing back actual memories?

The basic research I had uncovered on ECT side effects made no effort to distinguish among the many variables of human memory. It is relatively clear that the brain both routinely loses or has a break in the process of retrieval from long-term to working memory (Harrell et al., 1992), but also creates memory. Fiush (1996) points out the degree to which "we can be misled about our own memories" (see also, Crowley and Underwood, 1998; Payne and Blackwell, 1998). I had some limited familiarity with the work of Elizabeth Loftus on memory from research I had done years earlier as a young lawyer assisting in a murder case involving mistaken identity, and I knew the field had been pioneered when the issue of retrieved versus falsely created memory first became a debate in eyewitness identification cases and then in childhood sexual abuse prosecutions several decades ago, as noted by Alpert (1996). I had been fascinated then by what I learned about the brain and the inherent unreliability of our memory mechanisms.

As time goes by, earlier memories cued back after ECT seem more and more real to me, regardless of whether they ever were. Schooler (1996) observes that information integrated into memory can be held "with as much confidence as real memories" (see also Hirt et al., 1998; Moscovitch, 1989). This question is not a part of the studies assessing recovery of memory from ECT. For instance, while Sackeim (1992) summarizes the generally accepted description of the effects of ECT as being that, "The retrograde amnesia will often show a more gradual reduction, with substantial *return of memory* for events that were seemingly 'forgotten' immediately following the treatment course," (emphasis added), memory researchers such as Toglia (1996) point out instead that "The constructive nature of memory is sufficient to create recollections that are essentially entirely false" (see also Schooler, 1996).

The lack of connection between these fields also meant that I began a search that would last years to try to get memory assessment and help, when the resources should have been well known and available—and I should not have been the one to have to identify the need.

After that first significant experience of looking at basic ECT research, I became more anxious to gain a fuller understanding of what had happened to me. By the spring of 1997, I was in a more stable remission, and became eager to learn more about what was and was not known in whatever additional research I could track down. In doing so, I came to understand more fully the disparity in my case from standard statements about ECT, and I was increasingly frustrated in seeing how limited the data seemed on what the more serious effects could be.

Improved research was clearly not an easy task, particularly with the difficulty of devising tests to confirm the often random or isolated memory losses reported by many patients. The personal nature of perceptions, the complexity of human memory, and the processes of encoding, retrieval, and normal forgetting (Kellner, 1996; Cowley and Underwood, 1998; Payne and Blackwell, 1998), and the question of whether at the time testing is typically done the patient has gained an adequate sense of the degree of memory

to learn to live with it, I have become more relaxed in dealing with everyday situations that continue to arise. I find people almost universally helpful when typical encounters occur.

Woman on street (*in chance meeting*): "Anne! How wonderful to run into you. How are you?"

Anne (*rapid assessment: This is a person once well known, not a passing acquaintance who can be handled by bluffing through a conversation*): "Well, hello! Listen, I need to fill you in on something. I've been ill and a treatment I received has blocked my memory for several years back. I have to be honest. I have no idea who you are."

Woman: "Oh! Well, I'm Catherine S., from our time working together in New York in 1986."

Anne (*much relieved*): "Of course! Seeing you here out of time and place just threw me off. I remember now." (As well I did, from 9 years prior. I had just never expected to see her here in Burlington.)

Anne (*continues*): "Well, it's great to run into you here. What brings you to Burlington?"

Catherine: "I live in Burlington, remember?"

Anne: "No, I never knew that."

Catherine: "Well, actually, you did know that. We've had lunch together here several times over the past few years, and I've been out to visit you. It must be that treatment you mentioned."

I have never had a negative reaction to this kind of honesty. I do not necessarily go into a further explanation if I am having a passing encounter, but I do feel free to do so when there is time and supportive interest from the listener.

Despite acceptance and a growing comfort level in talking openly, despite the emotional outlet for anger through the development of my academic interest, and despite working through the experience of losing part of my sense of self, I remain bothered by a sense of incompleteness. It is obvious that if there is a serious side effect after heart surgery, there is follow-up intervention. The patient is checked for residual bleeding.

I had not been checked for residual bleeding. I feel left hanging—that nothing was ever comprehensively tested, recorded, or analyzed by the psychiatric profession and those involved in my care to evaluate my side effects: not just to intervene and to help me, but also to learn from my results. This should be routine when initial response shows significant cognitive impairment, as mine did. If it is done more adequately in other situations, the information, regardless, has not been collected and shared. No wonder the establishment has a different sense of the side effects. They don't ask.

I think that this lingering feeling of abandonment of care by the psychiatric profession, both as an individual and in a deeper sense on behalf of my peers, is strongly related to the part of me that still feels so damaged by my memory loss.

## CONCLUSION

My story is my own—what happened to me, and the care I did or did not receive cannot automatically be assumed to apply to the practice of ECT in the U.S.A. today or to the follow-up care delivered when severe side effects result. The broader existence of activist groups of former patients who, for whatever reasons, are disgruntled by their results

substantially higher-risk, pre-1985 procedure of dosing at a uniform, high level. Other practices exceeding recommended guidelines are documented by Reid et al. (1998). Thus my medical cost-benefit analysis in accepting ECT treatment was skewed from the start by the fact that the existing professional statements on potential risks did not match the actual risks presented by current mainstream practice.

The final issue is the information provided to the patient. As Sackeim (1992) notes, even though the reasons for the discrepancy between objective testing and subjective reports are unknown, "...in informing patients about ECT, it is important to relate that a few individuals report profound and long-lasting cognitive impairment that they attribute to this treatment modality." Kellner (1998) appropriately suggests that the key to improved informed consent is "a middle ground that does not appear defensive": disclosure both of ECT's powerful, lifesaving effects and its serious side effects, dealing with it in a way that eases apprehension and allows an informed choice between typically brief impaired functioning and a return to health (Kellner, 1996). While this goal has been clear at least since the 1990 Task Force report of the American Psychiatric Association, his belief that, "Nowadays, we *do* tell patients what to expect and everyone is better for it," (Kellner, 1996) is not yet a universal reality.

Because ECT involves a series of treatments during which the cost-benefit ratio continues to change and the patient's ability to participate in informed decision-making often continues to improve, while at the same time, memory of the original consent may become impaired (Consensus Conference, 1985), potentially contributing to patient perceptions that side effects were worse than expected (Bernstein et al., 1998), a better record available later to the patient of his or her own participation in the consent process (such as offering to audiotape or videotape, or having a family member or friend present), as well as written information for a follow-up cognitive assessment plan if needed, should also be provided (as an example of work with coping skills, see Harell, 1992). None of this was offered to me, and it was the lack of information, as much as the actual effects, which made recovery so difficult.

In addition, as Kellner (1996) so well summarizes, "Preparing a patient for the predictable, expectable, and largely stereotyped effects of ECT on memory and other domains of cognition is honest, necessary and helpful. It leads to realistic expectations for the treatment, and can help the patient and family prepare for the post-ECT period. Disappointment and fear are decreased and some practical steps towards restoration of memory (coaching, list-making and 'filling in' by family and friends) can be planned."

Without these advances—more comprehensive research regarding causes and rates of the most severe instances of memory loss, better transmission of new clinical information to practitioners, and more comprehensive, accurate information and follow-up for patients—a vital tool in the battle against life-threatening affective disorders will remain underutilized. It is a major social loss that should not have to be that way.

If sharing my own experiences of successful treatment but deeply troublesome side effects can help in that cause—if my voice is heard, and heard to speak for others like me—then my own sense of damage and abandonment will be assuaged. It will give my experience a value in the lives of others. It will not help my own memory to return, but it will ease the pain of the feeling that the damage may have been unnecessary to achieve the results.

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# EXHIBIT 39

Swartz 4-1-21
Exhibit 6



# warning statement revisited

13 messages

**Conrad Swartz** <cswartz@gmail.com> Wed, Nov 15, 2006 at 9:05 AM
To: Richard Abrams <richard.abrams@gmail.com>

Dick,
Additional reflection produced these thoughts.

The goals of the warning statement we need to make are 1) prevent lawsuits, and 2) not alienate psychiatrists.

All warnings that are written are stated in the form that "this product can (or may) cause xxxx." We should conform to this. Cigarette companies can not use a statement such as "nothing in this advertisement should be regarded as a statement that cigarettes do not cause cancer." This is not a warning

Loss of memories is more accurate than memory loss, which smells of dementia. Loss of memories is subjective and does not reflect brain damage.

Some ECT methods, such as traditional bilateral ECT, are associated with more forgetting than others.

I think these are the essential elements to consider in our statement.

A draft is below for you to consider, edit, etc.:

Some patients may experience some loss of memories with ECT, particularly with traditional bilateral ECT. This is a subjective symptom that does not specifically reflect observable brain structure. Illness, anesthesia, medications, and postponement of treatment have their own risks, which are substantial.

--Conrad

---

**Richard Abrams** <richard.abrams@gmail.com> Wed, Nov 15, 2006 at 9:52 AM
To: Conrad Swartz <cswartz@gmail.com>

Conrad,

Have a look at our website--I added a statement in 2 places: FAQs (Patients & Families) and "The Many Advantages.." (did I tell you this already?)

The problem with what you wrote is that it doesn't address the primary subject of all ECT lawsuits: failure to warn the patient that permanent memory loss can occur.

Dick

[Quoted text hidden]

---

**Conrad Swartz** <cswartz@gmail.com> Wed, Nov 15, 2006 at 10:31 AM
To: Richard Abrams <richard.abrams@gmail.com>

Dick,
The way it works is that companies publish their warning statements in documents to MDs, and this relieves their liabilities and takes care of duty to warn patients. These warning statements for drug companies appear in the PDR.

We don't appear in the PDR. So, we need to publish our warning statements in our literature and online.

The statement on the website is not adequate warning to deflect lawsuits. It **disclaims the warning itself** with the sentence, " Rarely, a patient has claimed severe, permanent memory loss, but such claims have not been substantiated by objective memory testing." This statement says there are no permanent memory effects. This is the opposite of what we need to state.

In view of your complaint about not using the word "permanent" in my draft I have put it in in this re-draft:

**Some patients may experience some temporary or permanent loss of memories with ECT, particularly with traditional bilateral ECT. This is a subjective symptom that does not specifically reflect observable brain structure. Illness, anesthesia, medications, and postponement of treatment have their own risks, which are substantial.**

Conrad

[Quoted text hidden]

---

**ıard Abrams** <richard.abrams@gmail.com> Wed, Nov 15, 2006 at 11:34
Conrad Swartz <cswartz@gmail.com>

ɔnrad,

ere's my revision of what you wrote.
uoted text hidden]

**Many patients experience temporary loss of recent or remote memories with ECT.doc**
20K

---

**ırad Swartz** <cswartz@gmail.com> Wed, Nov 15, 2006 at 1:46
Richard Abrams <richard.abrams@gmail.com>

Dick:

It looks like we are making progress, thank you.

Your draft did not say that permanent (or persistent etc) loss of memories can occur. This is a major omission and it opens up worrisome liability for us; there is no necessity for us to omit this. It is not our purpose to defend the field of ECT in our warning statement. It is our purpose to prevent lawsuits while not alienating psychiatrists, and this is all.

Loss of memories I understand, of course. I do not know what you are referring to by "memory functions." **Please explain what this is and how it differs meaningfully from loss of memories, or please remove it from the statement.** Finally, there is a difference between risks and adverse effects. In the statement below we can say either that risks are substantial, or that adverse effects can be substantial. Because you added "can be" I changed from risks to adverse effects.

==========draft start
**Many patients experience temporary loss of recent or remote memories with ECT, particularly with traditional bilateral ECT. A few patients have reported experiencing persisting loss of memories or memory functions after ECT. These are subjective symptoms and have not been related to observable structural brain changes. Mental and physical illnesses, anesthesia, medications, and postponement of treatment each have their own adverse effects, which can be substantial.**
==========draft end

I will not be able to work on this further until late Thursday or early Friday.

--Conrad
[Quoted text hidden]

---

**ıard Abrams** <richard.abrams@gmail.com> Fri, Nov 17, 2006 at 12:13
Conrad <cswartz@gmail.com>

ɔnrad,

ere it is again at your request.

ck
uoted text hidden]
uoted text hidden]

**Many patients experience temporary loss of recent or remote memories with ECT.doc**

---

Dick:

I had asked you to please reply to my e-mail, which I have now reprinted below. You merely sent me again the previous version. Perhaps my e-mail below never came to your sight.

--Conrad

[Quoted text hidden]

---

**Richard Abrams** <richard.abrams@gmail.com> Fri, Nov 17, 2006 at 9:52 AM
To: Conrad Swartz <cswartz@gmail.com>

Ah, yes--it was buried in the stack of messages one gets when doing a Gmail search, and which is shown without the first line of each message visible--very annoying, actually. The revision is fine--and memory functions are just that: acquisition, retention, retrieval, etc. (in contrast to memories, which are stored bits of information).

Dick

[Quoted text hidden]

---

**Conrad Swartz** <cswartz@gmail.com> Fri, Nov 17, 2006 at 10:13 AM
To: Richard Abrams <richard.abrams@gmail.com>

Dick,

Impairment of memory acquisition means impairment of learning. This is a dread claim, far worse than loss of memories. It is de facto amnestic disorder or dementia. If we are to include this in our statement we really need to be more specific about the evidence and the risk. I have not heard of permanent impairment of ability to learn after ECT. What is the evidence and risk of it?

Conrad

[Quoted text hidden]

---

**Richard Abrams** <richard.abrams@gmail.com> Fri, Nov 17, 2006 at 10:18 AM
To: Conrad Swartz <cswartz@gmail.com>

Conrad,

As you know, there is no scientific or objective evidence whatever of any permanent effects of ECT on any brain function--period. This disclaimer has only to do with what certain patients have claimed in their lawsuits, some of which have been lost by Mecta: permanent loss of memories and permanent loss of memory functions.

[Quoted text hidden]

---

**Conrad Swartz** <cswartz@gmail.com> Fri, Nov 17, 2006 at 10:21 AM
To: Richard Abrams <richard.abrams@gmail.com>

Dick,
I get it, OK.
So we are now agreed to proceed with the statement as it appears at the bottom of this e-mail.

[Quoted text hidden]

---

**Richard Abrams** <richard.abrams@gmail.com> Fri, Nov 17, 2006 at 10:48 AM
To: Conrad Swartz <cswartz@gmail.com>

Conrad,

Done (for the website at this point--I'll work with David on modifying the manual).

[Quoted text hidden]

---

**Conrad Swartz** <cswartz@gmail.com> Sat, Mar 14, 2020 at 2:00 PM
To: "c_swartz@yahoo.com" <c_swartz@yahoo.com>

[Quoted text hidden]

# EXHIBIT 40

*Ethical Human Psychology and Psychiatry*, *Volume 21*, *Number 2*, *2019*

# Electroconvulsive Therapy for Depression: A Review of the Quality of ECT versus Sham ECT Trials and Meta-Analyses

**John Read, PhD**
*University of East London, London, UK*

**Irving Kirsch, PhD**
*Harvard Medical School, Boston, MA*

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**Background:** Electroconvulsive therapy (ECT) is still being administered to approximately a million people annually. There have been no ECT versus simulated ECT (SECT) studies since 1985. The five meta-analyses of ECT versus SECT studies all claim that ECT is more effective than SECT for its primary target, severe depression. This review assesses the quality of those meta-analyses and of the 11 studies on which they are based. **Methods:** The meta-analyses were evaluated primarily in terms of whether they considered the quality of the studies they included, but also in terms of whether they addressed efficacy beyond end of treatment. The methodological rigor of the 11 studies included by one or more of the meta-analyses was assessed using a 24-point Quality scale developed for this review. **Results:** The five meta-analyses include between 1 and 7 of the 11 studies. The meta-analyses pay little or no attention to the multiple limitations of the studies they include. The 11 studies have a mean Quality score of 12.3 out of 24. Eight scored 13 or less. Only four studies describe their processes of randomization and testing the blinding. None convincingly demonstrate that they are double-blind. Five selectively report their findings. Only four report any ratings by patients. None assess Quality of Life. The studies are small, involving an average of 37 people. Four of the 11 found ECT significantly superior to SECT at the end of treatment, five found no significant difference and two found mixed results (including one where the psychiatrists reported a difference but patients did not). Only two higher Quality studies report follow-up data, one produced a near-zero effect size (.065) in the direction of ECT, and the other a small effect size (.299) in favor of SECT. **Conclusions:** The quality of most SECT–ECT studies is so poor that the meta-analyses were wrong to conclude anything about efficacy, either during or beyond the treatment period. There is no evidence that ECT is effective for its target demographic—older women, or its target diagnostic group—severely depressed people, or for suicidal people, people who have unsuccessfully tried other treatments first, involuntary patients, or children and adolescents. Given the high risk of permanent memory loss and the small mortality risk, this longstanding failure to determine whether or not ECT works means that its use should be immediately suspended until a series of well designed, randomized, placebo-controlled studies have investigated whether there really are any significant benefits against which the proven significant risks can be weighed.



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**Keywords:** electroconvulsive therapy; placebo; efficacy; meta-analyses; review; methodology

Electroconvulsive therapy (ECT) is still used on approximately a million people annually (Leiknes, Jarosh-von Schweder, & Hoie, 2012; Read, Bentall, Johnstone, Fosse, & Bracken, 2013). A review of 70 studies found, however, "large variation between continent, countries and regions in utilization, rates and clinical practice" (Leiknes et al., 2012, p. 296). For instance, a recent audit found a 12-fold difference in usage between the highest and lowest using regions of England (Read, Harrop, Geekie, & Renton, 2018).

The many recent studies that either compare ECT to other treatments, or compare different types of ECT with each other (Read & Arnold, 2017), typically open with an unqualified statement that ECT is a very effective treatment for depression. Some may consider these types of studies sufficient to justify the use of ECT. We contend, however, that, ECT must be assessed using the same standards applied to psychiatric medications and other medical interventions, with placebo-controlled studies as the primary method for assessment. There have, however, only ever been 11 placebo-controlled studies of the efficacy of ECT. The last study comparing ECT with sham/simulated ECT (SECT), in which the general anaesthetic is administered but the electricity is not, was 35 years ago (Gregory, Shawcross, & Gill, 1985). This review evaluates, for the first time, the impartiality and robustness of the meta-analyses of this small body of literature, and the quality of the studies cited in the meta-analyses. The primary goal is not to assess whether or not ECT is effective. The intent, instead, is to determine whether the available evidence is robust enough to answer that question.

## METHOD

A Medline (MESH) search for meta-analyses on the effectiveness of ECT for depression using placebo-controlled trials (ECT vs SECT), was conducted in June 2019, using the following index terms: ["ECT" OR "electroshock therapy" OR "electroconvulsive treatment" OR "electroshock treatment"] AND ["meta-analysis"] AND ["depression" OR "major depressive disorder"].

A 24-point Quality scale was developed to assess the studies cited by the meta-analyses. The scale combined the "risk of bias" domains of the *Cochrane Handbook Risk of Bias Tool* (randomization, blinding, incomplete outcome data and selective reporting; Higgins et al., 2011) with other criteria relating to quality of design and reporting, and some criteria specific to ECT research (see Table 1 for criteria and their definitions). No differential weightings were given to individual items, but the three key issues of randomization, blinding and diagnosis carried extra weight by virtue of having two or three items each. The 11 studies were independently rated, using the definitions in Table 1, by JR and LM, with each rater blind to the other's ratings. "Yes" indicated clear affirmative evidence. "No" meant either no evidence or clear negative evidence. Inconsistencies between raters were resolved by discussion and rereading the articles together. Spearman rank correlations and two-tailed *t* tests were used to assess the relationships between Quality scores and other variables.

**TABLE 1.** Definitions of the 24 Quality Criteria

| | |
|---|---|
| RANDOMIZED[a] | Any statement or evidence that the study was randomized, and no evidence that this was not the case |
| Process described | Any description of the randomization process |
| BLINDED[a] | Any statement or evidence that the study was blinded, and no evidence that the blind was broken—for raters or patients |
| Method tested | Any evidence that the blinding of either the raters or patients was tested |
| No previous ECT | None of the participants had had ECT at any time prior to the study |
| ALL DEPRESSED | All participants (or a clear subset with separate data) were adjudged, by any method, to be depressed (with or without other features, e.g., psychosis) |
| Reliable diagnosis | Diagnosis made by two or more independent people, or any standardized depression assessment tool, i.e., not just by one clinician/clinical diagnosis with unspecified diagnoser(s) |
| Severe | All participants *severely* depressed at outset of study, either any meaningful description of "severe," or ≤ 22 on Hamilton (44 if two raters, most studies), ≤ 29 on Beck scale) |
| FULL ECT COURSE | At least six ECTs or 6 SECTs; so excluding studies giving ECT to SECT group before six ECT treatments |
| SUICIDE MEASURE | Any outcome measure of suicide or suicidality (ideation) |
| VALIDATED DEPRESSION SCALE | e.g., Hamilton, Montgomery, Beck |
| Means and *SD*s | Means *and SD*s (or SEs or SEMS) reported for the depression scales pre and post treatment (or just the means and SDs of the *change* between pre and post) |
| NO SELECTIVE REPORTING[a] | Outcomes for all measures and all types of raters (e.g., doctors, patients etc.) reported |
| INDIVIDUAL PATIENTS' DATA | Any ratings/scores/categorization for individual participants reported |
| PATIENT RATINGS | Any self-report or patient ratings administered *and* scores reported |
| QUALITY OF LIFE MEASURE | Any "Quality of Life" ratings administered *and* scores reported (e.g., HONOS) |
| MORE THAN 1 RATER TYPE | More than one type/group of persons making separate ratings; e.g., psychiatrists, nurses, patients, etc. |
| DECLINERS DESCRIBED[a] | Any description of people who were approached but declined to participate |
| WITHDRAWALS DESCRIBED[a] | Any description of people who withdrew (or were withdrawn) from the study after it had started |
| OTHER TREATMENTS UNSUCCESSFUL | One or more other treatments (antidepressants, CBT etc.) had been tried and did not work prior to ECT |
| MEDS MATCHED/ CONTROLLED/ STOPPED | Psychiatric meds (e.g., antidepressants) were stopped for the study, or that the two groups (ECT and SECT) were matched or controlled in any way re. psychiatric meds |

(Continued)

**TABLE 1.** Definitions of the 24 Quality Criteria (Continued)

| | |
|---|---|
| BOTH ECT and SECT SAMPLES ≤ 10 | Both sample sizes (ECT and SECT) 10 or larger |
| AGE and GENDER REPRESENTATIVE | More than 50% female (but not all), and mean age of 50 or more |
| FOLLOW-UP DATA | Any outcome data gathered beyond end of treatment (more than 1 day after last ECT), without ECT being given to the SECT group |

***Note.*** ECT = electroconvulsive therapy; SECT = sham/simulated electroconvulsive therapy.
[a]Relates to one of the four Cochrane 'risk of bias' domains; either directly or, for DECLINERS DESCRIBED and WITHDRAWALS DESCRIBED, relates indirectly to the 'incomplete outcome data' domain.

## RESULTS

The search for meta-analyses produced 83 papers (see Figure 1). When the 83 papers were limited to ["SECT" OR "sham ECT"] etc., 14 remained. Three of these were literature reviews (Greenhalgh, Knight, Hind, Beverley, & Walters, 2005; Read & Bentall, 2010; Ross, 2006), one was a meta-analysis in Hungarian (Gábor & László, 2005), one was a meta-analysis of ECT versus SECT for older people only, discussed later (van der Wurff, Stek, Hooogendijk, & Beekman, 2003), and three were about transcranial magnetic stimulation. This left five meta-analyses for review (Janicak et al., 1985; Kho, van Vreewijk, Simpson, & Zwinderman, 2003; Mutz et al., 2019; Pagnin, de Queiroz, Pini, & Cassano, 2004; UK ECT Review Group, 2003). A follow-up search in March 2020 found no further meta-analyses or sham ECT studies.

### Independent Quality Ratings

The mean Quality scores of the two raters, for the 11 studies, 10.27 (*SD* 2.45) and 11.91 (*SD* 2.91), were not significantly different (T (20) = 1.42, $p$ = .17). Their scores for the 11 studies were significantly correlated (rho = .87, $p$ = .001). There were 55 inconsistencies out of the 264 ratings, representing an agreement rate of 79.2%. This translates to a *kappa* score (which allows for agreement by chance) of .58, in the "fair to good" range (.40–.75; Fleiss, 1981). The inconsistencies were resolved by discussion. The majority had resulted from raters missing (or misunderstanding) some text; for example, missing methodological information mentioned in a Results section, or missing results in a Discussion section. During this rereading of studies together some instances where both raters had missed some quality evidence were also discovered, and scores increased accordingly.

If ambiguity remained after discussion the raters erred on the side of "Yes." For example, one rater rated Lambourn and Gill "No" for "Means and *SD*s," whereas the other rated it "Yes" because the means were provided and the *SD*s, although not reported, could be calculated from individuals' data. This was finalized as "Yes." Brandon et al. (1984) reported means and *SD*s but only in the form of a graph, with no numbers, leading one rater to rate it as a "No." After discussion, a "Yes" was agreed. One rater had scored Ulett, Smith, and Gleser (1956) as "No" for "Reliable diagnosis" because it was not explicitly stated that

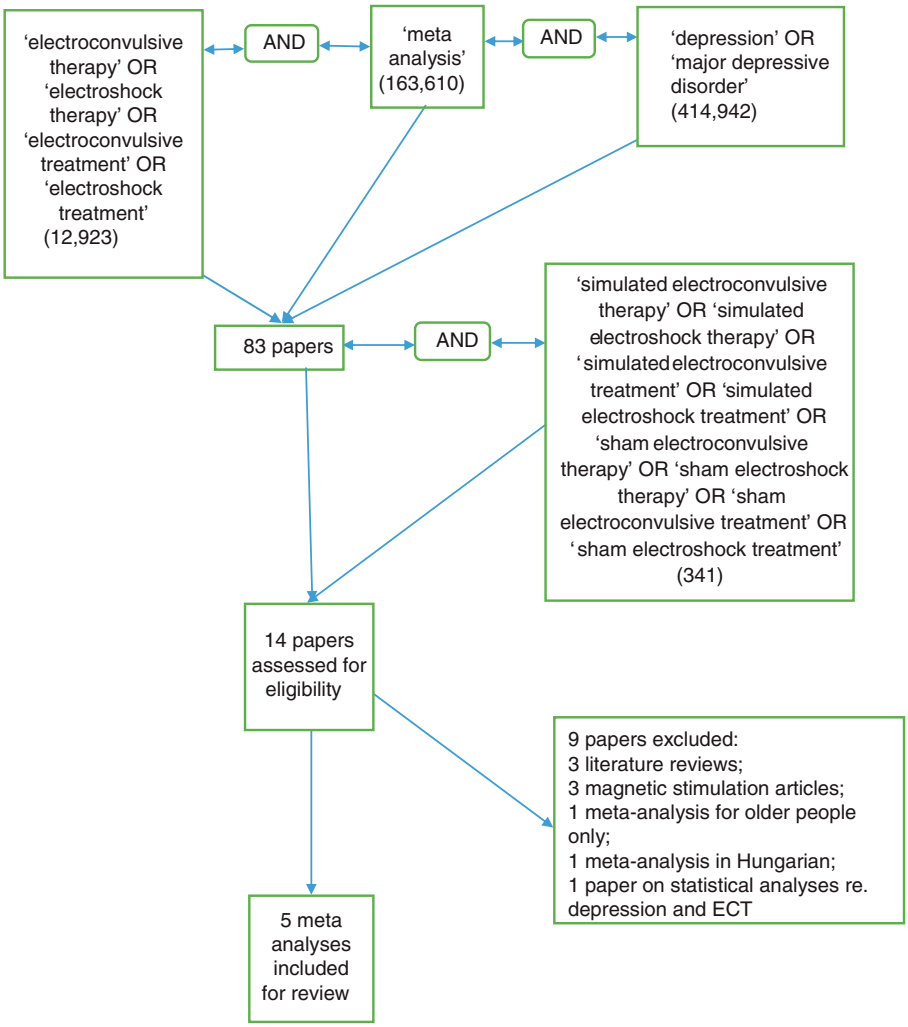


Figure 1. Flowchart of search strategy for meta-analyses.

diagnoses made in the study were independent; but a "Yes" was agreed on as there were two people diagnosing participants.

The mean of the final, agreed, scores was 12.27 (*SD* 3.20), somewhat higher than the original means of the raters.

### The 11 SECT versus ECT Studies Included in the Five Meta-Analyses: Findings at the End of Treatment

The 11 ECT versus SECT studies for depression cited by one or more of the five meta-analyses, summarized in Table 2, are the only 11 ever conducted. None since 1985 have

been identified by reviews (Read & Arnold, 2017; Read & Bentall, 2010) or the recent meta-analysis (Mutz et al., 2019). The first five were published between 1956 and 1963; with a second wave, of six, between 1978 and 1985. Three took place in the USA and the other eight in the UK, including all six of the later wave. So there have been no such studies in the UK for 35 years, none in the USA for 57 years, and none anywhere else ever.

***Ulett et al. (1956)—Quality Score 10/24.*** The first SECT versus ECT study, conducted in the USA, compared both ECT and "convulsive photoshock" (using flashing lights) to a sham treatment involving the same "light stage of sleep" as the two treatment groups. There was no significant difference between the ECT and SECT groups on the psychiatrist's ratings, with 33% and 24%, respectively, showing "recovery or marked improvement."

This study, however, does not belong in an evaluation of ECT for depression. The participants were "individuals with the types of mental illness which are thought to respond best to the shock therapies," in 1956. So 24 of the 42 (62%) in the ECT and SECT groups had diagnoses of "schizophrenic reaction" or "involutional psychotic reaction." The study also had no depression outcome measure. Despite this, and numerous other failings (see Table 3) two meta-analyses (Janicak et al., 1985; Pagnin et al., 2004) include this study. Pagnin et al. correctly report the difference between ECT and SECT as nonsignificant. The Janicak meta-analysis, however, wrongly report a significant difference in favor of shock therapy, by inappropriately merging the photoshock and ECT data.

***Brill et al. (1959)—9/24.*** The second study, also in the USA, did not assess outcome until a month after the treatment period so it really belongs as much with the follow-up studies (see below) as with the short-term/end of treatment studies. The study was included in the same two meta-analyses as the Ulett study. It involved 97 men with an average age of 35, so was unrepresentative of the modal ECT recipient—a woman in her 60s (Leiknes et al., 2012; Read et al., 2013, 2018). Only 30 were diagnosed with depression, but fortunately their data were reported separately. A positive outcome was deemed to be "recovery" on two-out-of-three tools: psychiatric evaluation, the Lorr Psychiatric Rating Scale (Lorr, Jenkins, & Holsopple, 1953), and psychological testing. None of the three explicitly assessed depression.

"Nearly half" of the participants had had ECT before, which may have contributed to the fact that "some patients in the nonshock group believed that they were receiving some new variation of ECT" (p. 628). This raises the possibility that some could tell that they may not have had real ECT, because of the absence of headaches and confusion immediately afterwards.

Sixteen of the 21 men in the ECT group (76%) and 4 of the 9 in the SECT group (44%) met the two-out-of-three criterion for recovery. The difference is not statistically significant.

***Harris and Robin (1960)—9/24.*** The first UK study was a trial of the antidepressant phenelzine, but included four women receiving ECT and four receiving SECT (all without phenelzine). The study invalidated any findings on ECT, however, by giving ECT to the SECT group after four ECTs (2 weeks). Despite this, and multiple other flaws (see Table 3), this study was included in two meta-analyses (Janicak et al., 1985; Pagnin et al., 2004). At the 2 week point two of the four ECT recipients and none of the SECT group had shown "great improvement." This difference was not statistically significant.

**TABLE 2.** Summaries of the 11 SECT vs ECT Studies, Outcomes at End of Treatment

| Study and Demographics | *n* ECT vs SECT | ECT Type<br>Frequency<br>% Previous ECT | Outcome Measure(s) | Results | Significant Difference | Two Most Serious Weaknesses |
|---|---|---|---|---|---|---|
| **Ulett et al. (1956)**<br>62% fem<br>17–66 years<br>mean 46 years | 21 vs 21 | Sine wave<br>Bilateral<br>Three per week<br>12–15 ECTs<br>29% | Psychiatrist Ratings of general improvement (1–5)<br>Malamud Scale (psychosis) | 33% vs 24% "recovery or marked improvement" | NO | 62% not depressed<br>No depression measure |
| **Brill et al. (1959)**<br>100% male<br>18–68 years<br>mean 35 years | 21 vs 9 | Sine wave<br>Frontotemporal<br>Three per week<br>20 ECTs<br>"nearly half" | Three rating scales of general improvement (1 month after treatment ended)"improved" = recovery on two of the three scales | 76% vs 44% "improved" | NO | No depression measure<br>All males, mostly middle-aged |
| **Harris and Robin (1960)**<br>100% fem<br>mean 62 years | 4 vs 4 | ?<br>?<br>Two per week<br>Eight ECTs<br>?% | General improvement scale (1–4) | 2/4 vs 0/4 "great improvement" | NO | Gave ECT to SECT group after 2 weeks (four ECTs)—invalidating end of treatment data<br>No depression measure |

(Continued)

**TABLE 2.** Summaries of the 11 SECT vs ECT Studies, Outcomes at End of Treatment (Continued)

| Study and Demographics | n<br>ECT vs SECT | ECT Type<br>Frequency<br>% Previous ECT | Outcome Measure(s) | Results | Significant Difference | Two Most Serious Weaknesses |
|---|---|---|---|---|---|---|
| **Fahy, Imlah, and Harrington (1963)**<br>55% fem | 17 vs 17 | ?<br>?<br>Two per week<br>Six ECTs | Doctors' rating scale (−1 to 3) | 35% vs 12% "recovered /minimal symptoms" | NO | No proper SECT group—no suggestion to control group that they might be having ECT |
| 30–59 years | | ? | Staff rating scale (−1 to 3) | %s not reported | NO[a] | Severe depression excluded |
| **Wilson, Vernon, Guin, and Sandifer (1963)**<br>100% fem | 6 vs 6 | ?<br>? | HAMILTON | 23 vs 10 points improvement | YES | One of the raters not blind |
| 40–59 years | | Two per week<br>Six ECTs<br>?% | MMPI-Dep (self-rated) | 29 vs 8 points improvement | YES | No older people, or men |
| **Freeman, Basson, and Crighton (1978)**<br>72% fem | 14 vs 18 | Sine wave<br>Bilateral<br>Two per week | HAMILTON<br>WAKEFIELD (self rating) | (no means or SDs—just graphs) | YES[b]<br>YES[b] | Gave ECT to SECT group after 1 week (2 ECTs)—invalidating end of treatment data |
| mean 52 years (range 20–70) | | 6.7 ECTs (mean)<br>56% | Visual analogue scale<br>BECK (self rating) | | YES[b]<br>NO[b] | 4/20 in ECT group (0/20 SECT) withdrew without improvement, not included in calculating means |

(Continued)

**TABLE 2.** Summaries of the 11 SECT vs ECT Studies, Outcomes at End of Treatment (Continued)

| Study and Demographics | *n* ECT vs SECT | ECT Type Frequency % Previous ECT | Outcome Measure(s) | Results | Significant Difference | Two Most Serious Weaknesses |
|---|---|---|---|---|---|---|
| **Lambourn and Gill (1978)** 56% fem | 16 vs 16 | Brief pulse Unilateral | HAMILTON | 26 vs 23 points improvement[c] | NO | 66% had had ECT before<br>Clinical diagnosis only |
| 36–69 years Mean 54 (11 ≤ 60, 34%) | | Three per week Six ECTs<br>66% | Doctor's Global assessment (0–3) | 6/16 vs 6/16[d] | NO | |
| **Johnstone et al. (1980)** 74% fem | 31 vs 31 | Sine wave Bifrontal | HAMILTON (psychiatrist) | 38 vs 28 points improvement | YES[e] | Blindness of raters not assessed |
| 30–69 years mean 49 years | | two per week Eight ECTs<br>21% | LEEDS (self rating) | not reported data | NO | No means or *SD*s reported[e] |
| | | | Nurses' Rating | not reported | NO | |
| **West (1981)** 59% male | 11 vs 11 | Sinewave Bilateral | Psychiatrists rating (0–100) | 48 vs 7 points improvement | YES | Blindness of raters not assessed |
| mean 53 years | | Two per week Six ECTs | BECK (self-rating) | 16 vs 2 points improvement | YES | Not severe depression |
| | | ?% | Nurses rating (1–9) | 5 vs 1 point improvement | YES | |

(Continued)

**TABLE 2.** Summaries of the 11 SECT vs ECT Studies, Outcomes at End of Treatment (Continued)

| Study and Demographics | *n* ECT vs SECT | ECT Type Frequency % Previous ECT | Outcome Measure(s) | Results | Significant Difference | Two Most Serious Weaknesses |
|---|---|---|---|---|---|---|
| **Brandon et al. (1984)** 64% fem | 43 vs 34 | Sine wave Bilateral | HAMILTON | 28 vs 12 points improvement | YES[e] | No means or SDs reported[f] |
| mean 54 years | | Two per week Eight ECTs (17% given less) | Psychiatrists' ratings (7 point scale of change) | 46 vs 25[g] | YES | 60% had had ECT before |
| | | 60% | "self-ratings" | not reported | ? | |
| **Gregory et al. (1985)** | 19 uni-lateral | Sine wave Unilateral and Bilateral | HAMILTON | 31 (uni), 28 (bi) vs 14 (SECT) points improvement | YES | Contradictory reporting of "withdrawers" (36%) |
| gender ? | 21 bilat-eral | Two per week approx. Eight ECTs | | | | Selective reporting of results |
| 35/60 60–64 years all under 65 | 20 SECT | ?% | MADRAS | 24 (uni), 25 (bi) vs 9 (SECT) points improvement | YES | |
| | | | "global assessment of depression" | Not reported | | |

***Note.*** ECT = electroconvulsive therapy; fem = female; SECT = sham/simulated electroconvulsive therapy.
[a]graphs show difference is even smaller for staff than for doctors. [b]after 1 week (2 ECTs). [c]Individual scores for each person given so means could be calculated. [d]rated 3 on a 0–3 scale. [e]Significant only for "deluded" and "retarded" subgroups. [f]Means and SDs reported by Buchan et al. (1992). [g]presumably for multiple raters on the 1–7 scale—not stated.

**TABLE 3.** Quality Ratings of the 11 Studies, on 24 Criteria

| | Ulett et al. (1956) | Brill et al. (1959) | Harris and Robin (1960) | Fahy et al. (1963) | Wilson et al. (1963) | Freeman et al. (1978) | Lam-bourn and Gill (1978) | John-stone et al. (1980) | West (1981) | Brandon et al. (1984) | Gregory et al. (1985) | x/11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 11 |
| RANDOMIZED | | | | | | | | | | | | |
| Process described | ✓ | ✓ | ✓ | ✖ | ✖ | ✖ | ✓ | ✓ | ✖ | ✓ | ✖ | 6 |
| BLINDED | ✓ | ✖[a] | ✓ | ✖[b] | ✖[c] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| Method tested | ✖ | ✓[d] | ✖ | ✓ | ✖ | ✓ | ✓ | ✓ | ✖ | ✓ | ✖ | 6 |
| No previous ECT | ✖ | ✖ | ✖[e] | ✖[e] | ✖[e] | ✖ | ✖ | ✖ | ✖[e] | ✖ | ✖[e] | 0 |
| ALL DEPRESSED | ✖ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 10 |
| Severe | ✖ | ✖ | ✓ | ✖[f] | ✓ | ✓ | ✓ | ✓ | ✖[g] | ✓ | ✓ | 7 |
| Reliable diagnosis | ✓ | ✖ | ✓ | ✖ | ✖ | ✓ | ✖ | ✓ | ✓ | ✓ | ✓ | 7 |
| SUICIDE MEASURE | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✓ | ✖ | ✖ | ✖ | ✖ | 1 |
| FULL ECT COURSE | ✓ | ✓ | ✖[h] | ✓ | ✓ | ✖[i] | ✓ | ✓ | ✓ | ✓ | ✓ | 9 |
| VALIDATED DEPRESSION SCALE | ✖ | ✖ | ✖ | ✖ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Means and *SD*s | ✓ | ✖ | ✖ | ✖ | ✓ | ✖ | ✓ | ✓ | ✓ | ✓[j] | ✖[k] | 6 |

(Continued)

**TABLE 3.** Quality Ratings of the 11 Studies, on 24 Criteria (Continued)

| | Ulett et al. (1956) | Brill et al. (1959) | Harris and Robin (1960) | Fahy et al. (1963) | Wilson et al. (1963) | Freeman et al. (1978) | Lam-bourn and Gill (1978) | John-stone et al. (1980) | West (1981) | Brandon et al. (1984) | Gregory et al. (1985) | x/11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NO SELECTIVE REPORTING | ✓ | ✓ | ✓ | ✖ | ✓ | ✓ | ✖ | ✖ | ✓ | ✖ | ✖ | 6 |
| INDIVIDUAL PATIENTS' DATA | ✓ | ✓ | ✓ | ✓ | ✓ | ✖ | ✓ | ✖ | ✖ | ✖ | ✖ | 6 |
| PATIENT RATINGS | ✖ | ✖ | ✖ | ✖ | ✓ | ✓ | ✖ | ✓ | ✓ | ✖[1] | ✖ | 5 |
| QUALITY OF LIFE MEASURE | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | 0 |
| MORE THAN 1 RATER TYPE | ✖ | ✖ | ✖ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✖ | 7 |
| DECLINERS DESCRIBED | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✓ | ✖ | ✓ | ✓ | 3 |
| WITHDRAWALS DESCRIBED | ✖ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 10 |
| OTHER TREAT-MENTS UNSUC-CESSFUL | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ | 0 |

(Continued)

**TABLE 3.** Quality Ratings of the 11 Studies, on 24 Criteria (Continued)

| | Ulett et al. (1956) | Brill et al. (1959) | Harris and Robin (1960) | Fahy et al. (1963) | Wilson et al. (1963) | Freeman et al. (1978) | Lam-bourn and Gill (1978) | John-stone et al. (1980) | West (1981) | Brandon et al. (1984) | Gregory et al. (1985) | x/11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MEDS MATCHED/ CON-TROLLED/ STOPPED | ✓ | ✖ | ✖ | ✓ | ✓ | ✖ | ✓ | ✓ | ✓ | ✓ | ✖ | 7 |
| BOTH ECT and SECT SAMPLES ≤ 10 | ✓ | ✖ | ✖ | ✓ | ✖ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 8 |
| AGE and GENDER REPRESEN-TATIVE[e] | ✖ | ✖ | ✖ | ✖ | ✖ | ✓ | ✓ | ✖ | ✖ | ✓ | ✖[m] | 3 |
| FOLLOW-UP DATA | ✖[n] | ✓ | ✖ | ✖ | ✖ | ✖ | ✓ | ✓ | ✖[o,p] | ✖[p] | ✖[p] | 3 |
| **SCORE OUT OF 24** | 10 | 9 | 9 | 9 | 12 | 13 | 17 | 17 | 13 | 16 | 10 | |

***Note.*** ECT = electroconvulsive therapy; SECT = sham/simulated electroconvulsive therapy.
[a]"some patients in the nonshock group believed that they were receiving some new variation of ECT." [b]patients and observers knew which treatment had been administered. [c]one of the raters not blind. [d]patients "blindness" tested; raters not. [e]percentage having had ECT prior to the study not reported. [f]"Moderate severity." "Severe depression with high suicidal risk were not included." [g]average baseline Beck scores in "moderate" depression range. [h]gave ECT to SECT group after 4 ECTs. [i]9 gave ECT to SECT group after 2 ECTs. [j]means and SDs represented in figure and published by Buchan et al. (1992). [k]means but no SDs. [l]self-rating scale administered but not reported. [m]gender and age not recorded. [n]not valid because sample mostly not depressed. [o]data gathered but only 5 days after last treatment. [p]most SECT patients had ECT during follow-up period, so no longer a SECT group.

***Fahy et al. (1963)—9/24.*** The second UK study was not a SECT study at all. It compared ECT to sleep induced by general anaesthetic, but: "No attempt was made to suggest to these patients that they were receiving ECT. As far as they knew, the sleep injection was a complete treatment in its own right" (p. 311). Despite this and numerous other flaws (see Table 3) this study was, again, included in the Janicak and Pagnin meta-analyses. Neither mentioned the absence of a SECT group when including the study in their effect-size calculations. The difference, in terms of percentage "recovered or minimal symptoms only" between ECT (35%) and SECT (12%), assessed by a doctor, was not statistically significant. Percentages were not reported for the staff's ratings (thereby meeting the Cochrane "risk of bias" criterion of "selective reporting"), but graphs show that the difference was even smaller than for the doctors. Both meta-analyses use the larger of the two differences in their calculations.

***Wilson et al. (1963)—12/24.*** This small USA project involved 12 ECT patients and 12 SECT patients, with half of each group on an antidepressant. The only meta-analysis to include this study (UK ECT Review Group, 2003) correctly reports only the data for the two groups of six not taking the antidepressant. On both the Hamilton (Hamilton, 1960) and the MMPI-Depression (Schiele, Baker, & Hathaway, 1943) scales the ECT group showed significantly more improvement than the SECT group. The meta-analysis fails to report that one of the two raters before treatment, and one of the three at the end of treatment, knew which patients had received which treatment, so the study was un-blinded. The ratings were not statistically different from each other, and were based on "the same interview" so it is quite possible that the blind raters were influenced by the nonblind rater. Multiple other failings are listed in Table 3, including the exclusion of people aged 60 or older, who are typical ECT patients.

***Freeman et al. (1978)—13/24.*** The first of the second wave of studies (1978–1985) occurred in Scotland. The only meta-analysis to include it was the one by the UK ECT Review Group. Like Harris and Robin (1960), this study invalidated any evaluation of the efficacy of a full course of ECT treatment by giving ECT to the SECT group before the end of the study (after just two ECTs). These two studies evaluate speed of response early in treatment but not efficacy of the whole treatment. After the two ECTs three clinician-rated scales recorded significant differences between the two groups, but there was no difference when the patients rated their own depression. The researchers (Freeman et al., 1978, p. 738) explained:

> The ideal design for such a trial would have been to have compared a full course of S.E.C.T. with a full course of real E.C.T.. . . We felt it ethically unjustified to withhold for a complete course a treatment generally regarded to be effective and to submit patients to perhaps unnecessary general anaesthesia. The method presented here was therefore a compromise.

Four of the 18 ECT patients, but none of the SECT patients, withdrew because they were "nonresponders," but they were not included when calculating means.

This was the only study to report whether participants had been tried on antidepressants prior to the study; 22 (54%) had not.

***Lambourn and Gill (1978)—17/24.*** This study was one of the two highest scorers for Quality. It provided individual Hamilton scores, plus doctors' ratings, for all 32 participants, who had been randomized to the ECT and SECT groups, matching for age and gender. The blindness of the raters was assessed and confirmed. The participants were representative of the age and gender mix of ECT recipients. Most (66%), however, had had ECT before, thereby increasing the probability of un-blinding for those patients.

The study differed from most studies by using unilateral, rather than bilateral, electrode placement. It also differed by studying people diagnosed with "depressive psychosis," although they were severely depressed. The following can be calculated from the individual scores. There was no significant difference in the mean reduction on the Hamilton scale (using the old scoring system in which the ratings of two raters are added together) between the ECT (26.2) and SECT (22.8) groups ($t$ (30) = .50, $p$ = .62). On the doctors' ratings 37.5% of both groups were rated 3 on an undefined 0–3 scale, and 69% of the ECT group vs. 62.5% of the SECT group were rated 2 or 3, a nonsignificant difference ($\chi^2$ = .14, $p$ = .71).

This study was included in all meta-analyses except the recent one (Mutz et al., 2019). Table 4 shows that four different effect sizes were calculated by the four meta-analyses, ranging from .17 (UK ECT Group, 2003) to 0 (Pagnin et al., 2004; Odds Ratio = 1.0). None of them reach the threshold of even a "small" effect size (.2; Hamilton, 1960).

***Johnstone et al. (1980)—17/24.*** The famous Northwick Park study was one of the largest studies, and is the other of the two highest scorers on the Quality scale. Neither the ratings by the nurses nor the self-ratings by the patients produced significant differences between the 31 ECT patients and the 31 SECT patients. There was, however, a significant difference on change in Hamilton scores rated by a psychiatrist. The reporting of the findings is problematic. There were no data or SDs reported for the two outcomes that found no significant difference between ECT and SECT (by nurses and patients), making them harder to include in meta-analyses. There was just one rather basic graph, for the psychiatrist's Hamilton ratings.

Furthermore, despite including three subtypes of depression Johnstone et al. (1980) failed to report separate findings for them. Re-analysis by Buchan et al. (1992) suggests that the difference between ECT and SECT on the Hamilton is only significant for the patients who were deluded as well as depressed (although it is hard to be sure because Buchan et al. (1992) merge the data for the sub groups with data from the Brandon et al. (1984) study).

Only one meta-analysis (UK ECT Group, 2003) includes this relatively rigorously conducted, but poorly reported, study.

***West (1981)—13/24.*** This small study was reported in just two pages, by a sole author. The 11 who received ECT were reported to have improved significantly more than the 11 receiving SECT, on separate ratings by psychiatrists, nurses, and patients. West concluded his findings were "very strong evidence" and that ECT is "an excellent treatment of severe depression." The differences were much larger than in any other studies. Unlike the other studies, there was virtually no change in the SECT group.

The nurses' scale raises concerns about the integrity of the study. The scale was described as a nine point scale from "very much worse" to "very much better," but scores were reported at baseline, before any treatment had taken place. One cannot be "worse" or "better" before a study begins.

**TABLE 4.** Summaries of the Five Meta-analyses of SECT versus ECT Studies

| META-ANALYSES | Janicak et al. (1985) | Kho et al. (2003) | UK ECT Review Group (2003) | Pagnin et al. (2004) | Mutz et al. (2019) |
|---|---|---|---|---|---|
| **Study** | **6 studies** | **2 studies** | **6 studies** | **7 studies** | **1 study** |
| | *n* = 205 | *n* = 109 | *n* = 226[a] | *n* = 245 | *n* = 77 |
| Ulett et al. (1956) | $\chi^2$ = 6.36*,[b] | | | *OR* = .57 | |
| Brill et al. (1959) | $\chi^2$ = 2.37 | | | *OR* = 3.82 | |
| Harris and Robin (1960) | $\chi^2$ = .67 | | | *OR* = 17.0 | |
| Fahy et al. (1963) | $\chi^2$ = 1.09 | | | *OR* = 3.76 | |
| Wilson et al. (1963) | | | ES = 1.08 | | |
| Freeman et al. (1978) | | | ES = .63 | | |
| Lambourn and Gill (1978) | $\chi^2$ = .12 | ES = .09 | ES = .17 | *OR* = 1.00 | |
| Johnstone et al. (1980) | | | ES = .74* | | |
| West (1981) | $\chi^2$ = 14.85* | | ES = 1.25* | *OR* = 86.1* | |
| Brandon et al. (1984) | | ESs = 1.38 – 1.99* | | *OR* = 2.16 | No data |
| Gregory et al. (1985) | | | SES = 1.42* | | |
| Overall finding of meta-analyses | 72% v 40% $\chi^2$ = 21.54 $p$ < .001 | Pooled Effect Size = .95 [95% CI .35–1.54] | Pooled Effect Size = .91 [95% CI · 54–1.27][c] | *OR* = 2.83 [CI 95% 1.30–6.17] $\chi^2$ = 6.87 $p$ = .009 | *ORs* Bilateral[e] = 8.91* High-dose unilateral[f] = 7.27* Low dose unilateral[f] = 2.74 Bifrontal[f] = 3.39 |
| | 2/6 studies significant[d] | 1/2 significant | 3/6 significant | 1/7 significant | 2/4 types significant |

***Note.*** Empty cells indicate study excluded by meta-analysis. ECT = electroconvulsive therapy; SECT = sham/simulated electroconvulsive therapy. *OR* = odds ratio between ECT and SECT; ES = standardizsed effect size.

[a]reported as 256 by UK ECT Group, by including withdrawers during four of the studies. [b]wrongly included photoshock data, without which the finding is nonsignificant. [c]"translates to" a mean Hamilton difference of 9.7 (95% CI 5.7–13.5). [d]same year as the meta-analysis so possibly not published in time. [e]extrapolated from one ECT–SECT study (Brandon et al., 1984) and multiple other (not ECT–SECT) studies. [f]no data in the only ECT–SECT study (Brandon et al., 1984) to directly support these *ORs* (see text).
*statistically significant finding.

One patient from each group was withdrawn in week one due to "lack of improvement." If both had been scored as 0 improvement, rather than excluded, this would, in such small groups, have slightly reduced the difference in mean improvement scores between the two groups. For example, the difference between the ECT and SECT groups in the mean amount of change in the psychiatrist's ratings would have fallen from 41.1 (48.4 vs 7.3) to 37.7 (44.4 vs 6.7). An additional ECT patient was withdrawn in week one because s/he "could not complete the Beck Depression Inventory." This person was withdrawn *after* baseline assessments so they must have become unable to respond (to written questions on a 0–3 scale) *after* one or two ECTs. So while it appeared that 11 out of 11 ECT patients improved significantly, the true proportion was 11 out of 13.

Despite the assertion that "These findings confirm the value of electric convulsion therapy in severe depressive illness," the two groups had average baseline Beck scores of only 24 and 27, which are within the "moderate" range of depression (20–28; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The baseline scores for the psychiatrists' ratings, on a scale with 100 representing "most severe depressive illness," were only 68 and 71.

Brandon et al. (1984; reviewed next), commenting on the West study, raise concerns about "The sample size, the unusually unequivocal result, problems of selection, and doubts about the extent to which blindness was achieved" (p. 23). West did not tell us how blindness was achieved by either "the psychiatrist in charge" or by the "nurses." We were not told how many nurses were raters, or anything about their role in treatment. We were not told how many patients had enhanced probability of knowing whether they had received ECT in the study because they had had it before. The "blindness" of the raters was not assessed.

Despite all these failings three meta-analyses include this study (using the data that ignored the two withdrawals), and use its aberrantly large pro-ECT findings in their calculations (Janicak et al., 1985; Pagnin et al., 2004; UK ECT Review Group, 2003).

***Brandon et al. (1984)—16/24.*** The largest of the 11 studies (77 patients) took place in Leicester, England. It was a relatively high quality study. The samples were typical of ECT recipients in terms of depression severity, gender, and age. The blinding process was described and tested. Apart from failing to report means and SDs (provided later by Buchan et al., 1992), other failings included the fact that 60% had had ECT before (thereby reducing the probability of genuinely blind ratings by the patients) and that the patients' self-report scores were not reported. No explanation is given for this selective reporting.

On both the Hamilton and a psychiatrist's rating scale the 43 in the ECT group improved significantly more than the 34 in the SECT group. Analysis by Buchan et al. (1992), of the Brandon et al. (1984) and Johnstone et al. (1980) studies combined, however, found that the differences in Hamilton scores were only significant for patients who were "deluded" or "retarded" (slowed thoughts), which was less than half of the participants in the two studies (45%; Buchan et al., 1992, p. 357). None of the three meta-analyses that include the Leicester study (or the one that includes Johnstone's Northwick Park study) acknowledge this. Nor do they wonder why the patients' ratings were not reported.

***Gregory et al. (1985)—10/24.*** The last ever ECT versus SECT study took place 35 years ago. The "Nottingham ECT Study" actually had three groups. The ECT participants were divided into two groups by electrode placement (unilateral or bilateral). It is almost impossible to make sense of the findings. "Of the 69 patients entering the study, 25 received fewer than six study treatments; these were classed as withdrawers" (Gregory et al., 1985,

p. 521). Of these 25 14 were withdrawn because of "failure to improve" and five because they "were better." So 19 of the 69 participants (27%) in a study designed to determine who got better were withdrawn because they did, or did not, get better. (Three of the withdrawers in the ECT group, but none in the SECT group, withdrew consent after the study started.) To further confuse matters Table 1 in Gregory et al. (1985) reports the mean scores of 60 people with "complete data available" although there were only 44 participants remaining after the 25 were withdrawn. A graph portraying changes on the Montgomery–Asberg depression scale (MADRAS; Montgomery & Asberg, 1979) seems to have numbers for each of the three groups closer to those expected when subtracting the withdrawers. Their Table reports "percentage changes" that are more than twice as *large* for the SECT group as for either of the two ECT groups, on both the Hamilton and MADRAS. Finally, a "global assessment of change in depression" was made, but not reported (thereby meeting the Cochrane criterion of "selective reporting").

A Cochrane review on ECT for "the depressed elderly" set out to calculate an effect size for the 35 participants over the age of 60 in this study but found, unsurprisingly, that insufficient data had been provided to make that possible (van der Wurff et al., 2003).

The only meta-analyses that includes this study (UK ECT Group, 2003) fails to acknowledge any of these major problems and unquestioningly included the strong finding in favor of ECT in their calculations of effect sizes.

## Follow-Up Findings

Seven of the 11 studies provided follow-up data, but we shall see that only three produced meaningful data for comparing ECT and SECT. An eighth study had stated "We hope to report longer-term effects in a later article" (Fahy et al., 1963, p. 310), but they didn't.

***Ulett et al. (1956).*** Six months after the end of treatment a comparison was made using patients who had been discharged and not received ECT after the end of the study period. Four of the 11 who had had ECT (36%) had relapsed, compared to none of the four in the SECT control group. The majority of patients in this study, however, did not have a depression diagnosis so this finding is irrelevant to the current review.

***Brandon et al. (1984) and Gregory et al. (1985).*** Neither Brandon et al. (1984; 2 and 6 months follow-up) nor Gregory et al. (1985; 1 and 6 months) found significant differences between ECT and SECT at follow-up. Moreover, both studies invalidated any evaluation of long-term benefits by giving ECT to most of the SECT group during follow-up. Brandon et al. (1984), gave ECT to 20 of its 34 SECT participants, and to 17 of the 42 in the real ECT group, during follow-up. Gregory et al. (1985) gave an average of 4.1 ECTs to their SECT group and 1.5 to their ECT group during follow-up.

***West (1981).*** West reported psychiatrists' scores on a 0–100 scale (but not the nurses' or patients' scores), 5 days after the last treatment. The difference in the size of change from baseline was an enormous 53.6 points (52.1 vs −1.5). If such data can be believed they would produce a rather incredible effect size (Cohen's *d*) of 3.22. We have already noted the serious methodological failings of, and ominous questions about, this study.

West then followed up for a further 3 weeks, but like Brandon et al. (1984) and Gregory et al. (1985) gave ECT to most of the SECT group (10 of the 11).

Further suspicion about this study comes from the fact that at the end of the first part of the study the mean psychiatrists' score for the 11 SECT patients was 63.4, but the "base" mean score for the follow-up study, for the 10 remaining SECT patients, was reported to have jumped to 73.4. This is not mathematically possible by excluding just one of 11 people.

***Brill et al. (1959).*** This early USA study did not assess outcomes till a month after treatment ended. As we have seen, 16 of the 21 men in the ECT group (76%) and 4 of the 9 SECT patients (44%) met the researchers' criterion for recovery. The difference is not statistically significant ($\chi^2$ = 2.86, p = .09). The effect size (*d*) is .297 (95% CI −0.44–1.04). This study had extensive methodological flaws, scoring only 9/24 on the Quality scale. As noted earlier, it involved 97 men with an average age of 35, so was totally unrepresentative of the modal ECT recipient—a woman in her 60s. None of the outcome measures explicitly assessed depression. "Nearly half" of the participants had had ECT before.

***Lambourn and Gill (1970).*** Lambourn and Gill also followed up participants for a month. Because they reported detailed data for individual patients it is possible to calculate mean outcomes for the seven ECT patients and eight SECT patients who did not have ECT during the follow-up month. The researchers used a 67% or greater improvement (from baseline) on Hamilton scores as an indicator of improvement. This was achieved, at 1 month follow-up, by four of the seven ECT patients (57%) and five of the eight SECT patients (62%). The mean reductions in Hamilton scores were 30.57 (*SD* = 18.61) for the ECT group and 35.75 (*SD* = 17.65) for the SECT group, producing a difference of 5.18 and an *SD* for the whole sample of 18.10, which produces a "small" effect size (*d*) of .299, in favor of SECT.

(The researchers failed to report their data on number of hospital days during follow-up.)

***Johnstone et al. (1980).*** Johnstone et al. assessed at 1 month and 6 months posttreatment, on three scales. There had been a significantly greater drop in Hamilton scores at the end of treatment for the ECT group, but:

> The advantage of real over simulated ECT was not retained and at the one-month and six-month follow-ups the Hamilton scores of the two groups were almost the same. The Leeds self ratings showed similar trends but these were never significant, and this was also true of the ratings by nurses. (p. 1318)

So none of the three sets of raters found a significant difference between ECT and SECT at one or 6 months after the end of treatment. Johnstone et al. (1980) reported no specific follow-up data, just graphs. Buchan et al. (1992), however, provided Johnstone et al.'s (1980) 6 months mean improvement scores on the Hamilton (but not the nurses' or patients' ratings). The mean reductions were 36.33 for the ECT group and 35.30 for the SECT group. Calculating an effect size for this small difference (1.03 points) is problematic, as we do not know the SDs. The SEs for the data at the end of treatment (3.0 for ECT and 2.7 for SECT) translate into SDs of 16.70 and 15.03 respectively ($SD = SE \times \sqrt{N}$). If we use those as estimates of the SDs after 6 months, the 1.03 difference between the amount

of change in the two groups translates into an effect size of .065. This does not approach the .2 level for a "small" effect size (Cohen, 1988).

Brandon et al. (1984) concluded (p. 23):

> The well designed and carefully-controlled clinical trial. . . (Johnstone et al., 1980) showed that electroconvulsive therapy had only a small effect in depression at the end of the trial period and there was no difference in the condition of patients given real and simulated treatment at one and six months of follow up.

Johnstone et al. (1980), themselves, emphasized this point (p. 1319):

> The most striking finding is that the differences which were present at the end of the course of eight treatments had disappeared one month later and were undetectable also at six months

***Conclusion Regarding Long-Term Efficacy.*** A conservative conclusion from the four studies that provided some relevant data would be that there is no evidence that ECT has any lasting benefits beyond 5 days. Given all the problems with the West study it seems reasonable to exclude it from considerations and conclude that there is no robust evidence of ECT having any benefit at all beyond the last day of treatment.

If we consider only the three studies with data for at least 1 month we are left with one small effect size, .297, in favor of ECT (Brill et al., 1959), one study with a trivial effect size, .065, in favor of ECT (Johnstone et al., 1980) and one with a small effect size, .299, in favor of SECT (Lambourn & Gill, 1978). If we exclude the Brill study because of its multiple methodological flaws (not least its failed blinding process, and its being based on a very atypical sample of middle-aged men) we are left with Lambourn and Gill and Johnstone et al., (1980) two of the three highest Quality studies. Neither of these two studies, one with unilateral electrode placements and one with bilateral, provide any evidence of any long-term benefits of ECT compared to SECT.

## The Five Meta-Analyses

The first meta-analysis (Janicak et al., 1985) was published in 1985, possibly too early to consider the last study (Gregory et al., 1985). Three meta-analyses were published nearly 20 years later, in 2003 or 2004. The last was published in 2019. All five concluded that ECT is more effective than placebo.

The five meta-analyses include, between them, the 11 ECT versus SECT studies described above. Table 4 shows the marked variation in the number of studies included in the meta-analyses, from one (Mutz et al., 2019) to seven (Pagnin et al., 2004). No study was included in all five meta-analyses. Most (eight) were included in just one or two meta-analyses.

***Janicak et al. (1985).*** *Inclusion Criteria.* The first meta-analysis, by Janicak and colleagues, includes six studies (Table 4). The "most important" inclusion criterion is the ability "to determine each patient's response to treatment" (p. 298), and "the assessment of each patient's response was determined by the author's designation of the patient as a responder or nonresponder" (p. 298). Five of the six included studies meet the criterion

(see Table 3). One study does not but is included anyway; the one with the strongest outcome in favor of ECT (West, 1981). Although West recorded that it was considered "therapeutically desirable" (without stating by whom or by what criteria) for 10 of the 11 SECT patients to receive ECT in the second part of his study, he neither reported any scores or categorizations for individual patients nor designated participants as "responders." A second criterion is "systematic method for diagnosing the patient as depressed." This is not the case for three of the six (Table 3). A third criterion is that depression be "severe." Only two of the six studies met this criterion (Harris & Robin, 1960; Lambourn & Gill, 1978). One stated "Severe depressions with high suicidal risk were not included" (Fahy et al., 1963, p. 310).

*Quality Control.* Janicak et al. (1985) make no attempt to evaluate the methodological rigor of the six studies. They are either unaware of, or actively ignore, the 72 specific instances of methodological failings across the six studies (see Table 3). The six included studies had a slightly lower mean Quality score (11.17) than the five excluded studies (13.60), but the difference is not significant ($t$ (9) = 1.30, $p$ = .26).

*Short-Term Findings.* Efficacy was calculated "by taking the difference in percentage efficacy between real ECT and SECT and averaging across all studies." The reviewers report an "overwhelming statistical superiority of ECT over SECT" (Janicak et al., 1985, p. 301).

The totals they report from their six studies are 72% for ECT and 40% for SECT; hence the assertion that ECT is "32% more effective" (Janicak et al., 1985, p. 298). This is an incorrect calculation of the two percentages from their own Table (Janicak et al., 1985, p. 299). The numbers are, for ECT 73/109, which is 67% not 72%: and, for SECT, 33/96, which is 34% not 40%. These errors do not significantly alter the overall difference between the two conditions, but do indicate carelessness.

More importantly, the reported percentages of two of the six studies are incorrect. In their report of the Ulett et al. (1956) study, Janicak et al. (1985) wrongly include the data of patients subjected to photoshock. Without these patients the correct figures are ECT 7/21 (33%) versus SECT 5/21 (24%), a 9% difference, compared to a 30% difference (65% vs 35%) when the photoshock participants are included. Secondly, Brill et al. (1959) had reported (p. 630; Table 3) that the percentages meeting their criterion of showing improvement on two of their three measures as 76% "shock" versus 44% "nonshock" (16/21 vs 4/9). Janicak, however, report 67% versus 25% (p. 299; Table 1), thereby inflating the difference between real and SECT from 32% to 42%. The percentages using the *correct* numbers for the five studies that *did* report percentages of "responders" (i.e., excluding West, 1981—see above) are: ECT 45/79 (57%) versus SECT 25/67 (37%), a difference of 20%, rather than 32%. This is statistically significant ($\chi^2$ = 5.61; $p$ < .05), but not as strongly as Janicak's claim of $\chi^2$ = 21.54 ($p$ < .0001).

Four of their six studies (Brill et al., 1959; Fahy et al., 1963; Harris & Robin, 1960; Ulett et al., 1956) have the most methodological flaws of the 11 studies (see Table 3), all four having a Quality score of 10 or less out of 24 (see Table 3).

*Follow-up Findings.* Janicak et al. (1985) acknowledge that "questions such as those raised by" Johnstone et al. (1980) when they found no difference at follow-up are "left unanswered" (p. 301).

***Kho et al. (2003).*** *Inclusion Criteria.* Eighteen years later Kho et al. (2003) published their meta-analysis in the *Journal of ECT.* It was based on just two studies. They excluded all pre-1978 papers, because of their diagnostic ambiguities (p. 140) and because they wanted to

determine "whether the superior efficacy of ECT is still found using more recently published studies" (p. 140). This assumption, that ECT had already been shown to have "superior efficacy," might be considered a sign of bias on the part of the authors.

Kho et al. (2003) set out to include only studies reporting means and standard deviations generated with depression rating scores such as the Hamilton (1960). They exclude two studies which meet this criterion (Johnstone et al., 1980; West, 1981), without explanation, and rely instead on just two studies (Brandon et al., 1984; Lambourn & Gill, 1978).

*Quality Control*. Kho et al. (2003) assess the quality of the studies on a 0–5 scale based on randomization, double-blindness and description of withdrawals. Eight of the sixteen various types of studies included in their broader meta-analyses scored 0 out of 5. They fail, however, to report the scores of individual studies.

This is the only meta-analysis where our 24-point Quality scale produces a significantly higher mean score for the included studies (16.50) than the excluded studies (11.33); ($t$ (9) = 2.59, $p$ = .029).

*Short-term Findings*. The two studies, involving 59 ECT patients and 50 SECT patients, produced four effect sizes. The reviewers calculate a pooled effect size (delta) of .95 (95% interval—-0.35 to +1.54). The reported effect sizes for the three subtypes of depression in the Brandon et al. (1984) study range from 1.38 to 1.99, all far higher than the .77 calculated by Pagnin for the three subtypes combined. Kho et al. (2003) acknowledge that "because the three ESEs from the Brandon study may be correlated, the results from the comparison between ECT and SET may be exaggerated" (p. 145). So three of the four effect sizes may have been "exaggerated" and the fourth (Lambourn & Gill, 1978) was calculated as .09.

Kho et al. (2003) fail to mention any of the problems of the two studies listed in Table 3, including the fact that in the Brandon et al. (1984) study 60% had had ECT before (thereby significantly compromising the blindness of the ratings by the patients) and that the patients' self-report scores scale were not reported.

*Follow-up Findings*. The issue of efficacy beyond the end of treatment was not mentioned.

***UK ECT Review Group (2003).*** In the same year, 12 reviewers, led by Oxford University psychiatrists, published a meta-analysis funded by (but independent from) the UK Department of Health, and published in the *Lancet*. It is the only one of the four meta-analyses published at the time that was considered to be a "good-quality systematic review of randomized evidence" by a subsequent 170-page UK report for the National Health Service (Greenhalgh et al., 2005).

*Inclusion Criteria*. The "primary outcome" is "a continuous depressive symptoms scale" but "dichotomous data are merged to produce estimates of odds ratios" and the two are combined using "numerical simulation techniques based on Gibbs sampling" (p. 800).

Six of the 11 studies are included (see Table 4). Freeman et al. (1978) and Harris and Robin (1960) are included despite having invalidated their findings by giving ECT to the SECT group. There is no explanation for excluding four of the other five (although Table 3 shows there are good reasons to do so). Brandon et al. (1984) is excluded "because 43 patients had nondepressive diagnoses" (p. 806). This is incorrect. The 43 had been omitted from the study.

*Quality Control.* Greenhalgh et al. (2005, p. 15) note that "Little information was provided in the review (UK ECT Review Group, 2003) regarding the characteristics of participants in terms of the nature and severity of their condition, medication history and previous use of ECT." Quality is, however, evaluated, using four criteria: "reporting of allocation concealment, masking, loss to follow up, and length of follow up" (p.799). The UK ECT Group do comment that "The quality of reporting of the trials was poor" (p. 801), but fail to report the performance of individual studies. The reviewers acknowledge the small sample sizes and the absence of data on patients who are "most likely to receive it—e.g., older patients . . ." (p. 806). They are, however, unaware of, or actively ignore, the 47 other specific instances of methodological failings across their six studies (see Table 3).

The quality of the six included studies does not differ significantly from that of the five excluded studies (13.67 vs. 10.60; $t$ (9) = 1.74, $p$ = .12).

*Short-term Findings.* Unlike the other meta-analyses, which all presuppose that ECT is effective, these reviewers start by acknowledging that views vary, from "it is probably ineffective but certainly causes brain damage . . . through to those who think it is the most effective treatment available in psychiatry and is completely safe" (p. 799).

This is the only meta-analysis to include the Johnstone et al. (1980) study. Only the statistically significant outcome (Hamilton ratings by a single psychiatrist) is included. The nonsignificant findings, from the nurses' and patients' ratings, are ignored, without explanation.

This is also the only meta-analysis to include Freeman et al. (1978). It doesn't mention that ECT was given to SECT patients after a week, or that 20% of ECT patients withdrew unimproved.

The two studies with the largest effect sizes (Gregory et al., 1985; West, 1981) both have multiple methodological shortcomings (see above and Tables 2 and 3).

Ignoring all these problems the reviewers go on to combine the categorical and continuous outcome data to produce a pooled effect size of .91 in favor of ECT. The other four meta-analyses reached a generalized, unqualified conclusion that ECT "is effective." Although the the UK ECT Group (2003) also concluded that "In the short-term (ie at the end of treatment), ECT is an effective treatment for adult patients with depression" (p. 806), they added:

> There is limited randomised evidence on the efficacy of ECT in the specific subgroups of patients who are presently most likely to receive it—eg, older patients or those with treatment-resistant illnesses—or in subgroups of patients in whom ECT is thought to be especially effective. (p. 806)

Multiple emails were sent by JR to the lead author, Professor John Geddes, and other members of the UK ECT Review Group, seeking clarification about all the concerns raised above. Despite polite acknowledgements of the emails none of the questions were answered.

*Follow-up Findings.* This was the only meta-analysis to investigate longer-term efficacy. Only one study is identified (Johnstone et al., 1980) and "a non-significant two-point difference in final HDRS (Hamilton, 1960) was noted in favour of the simulated group" (p. 801). This is potentially misleading, in favor of SECT. Although the SECT group did end up two points lower, the ECT group had started off more depressed and had actually

changed 1.03 points more than the SECT group (Buchan et al., 1992, p. 358, Table 2), but neither difference is statistically significant.

***Pagnin et al. (2004).*** *Inclusion Criteria.* The fourth meta-analysis was published in the *Journal of ECT*. It includes the largest number of studies, seven, and the largest number of people, 245. Like Janicak et al. (1985), the reviewers include only studies from which they could "determine each patient's response to treatment, using author's own criterion of response or no response." (p. 13), correctly excluding Freeman et al. (1978), Johnstone et al. (1980), and Gregory et al. (1985) on that basis, but, like Janicak et al. (1985) and the UK ECT Review Group, dubiously including West.

*Quality Control.* Pagnin et al. (2004) make no attempt to rate studies in terms of methodological rigor. The difference between the mean Quality scores of the seven included studies (11.86) was not significantly different from that of the four excluded studies (13.00), ($t$ (9) = .55, $p$ = .60). The reviewers acknowledged problems with "diagnostic heterogeneity," randomization, and maintaining blindness, but without naming any specific studies. They were unaware of, or actively ignored, the 74 other specific instances of methodological failings across the seven studies (see Table 3).

*Short-term Findings.* Despite only two of the seven studies (Brandon et al., 1984; West, 1981) producing a significant difference, the studies do, when combined, find a significantly greater mean effect size for ECT than for SECT at end of treatment ($\chi^2$ = 6.87, $p$ = .009). Four of the seven included studies had the four lowest Quality scores of the 11 (see Table 3; Brill et al., 1959; Fahy et al., 1963; Harris & Robin, 1960; Ulett et al., 1956) and were excluded by three of the other meta-analyses (Kho et al., 2003; Mutz et al., 2019; UK ECT Group, 2003) (see Table 3). It is also unclear how the effect sizes were calculated. For example Pagnin et al. (2004) report an effect size (D) of 1.341 for the Brill et al. (1959) study (Table 3, p. 15). Yet the 16/21 versus 4/9 improved ratios actually produce an effect size (D) of .297 (95% CI −0.44–1.04; using www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD9.php; see Table 4).

The reviewers acknowledge that any advantage of ECT over SECT is only "specifically among patients with delusions and/or retardation [slowness of thought]" (p. 19).

*Follow-up Findings.* The absence of any evidence of efficacy beyond the end of treatment is, again, not mentioned.

***Mutz et al. (2019).*** *Inclusion Criteria.* The most recent meta-analysis, from the *Institute of Psychiatry* in London, appeared 15 years later, in the *British Medical Journal* (Mutz et al., 2019). It differs from previous meta-analyses in being a network meta-analysis, making pair-wise comparisons, between four types of ECT and 14 types of brain stimulation, and, when possible, comparing these to sham placebo treatments.

Inclusion criteria required use of the Hamilton or Montgomery scales and a manual-based diagnosis of "major depressive disorder" or "bipolar depression." Outcomes were efficacy and discontinuation/acceptability. Only 2 of the 11 studies were included (Brandon et al., 1984; Gregory et al., 1985). Although not immediately apparent from the article, only one study (Brandon et al., 1984) actually contributed to the analysis regarding efficacy.

A personal communication (Mutz et al., 2019) responding to multiple questions from JR, explained: "The Gregory et al. (1985) study only contributed to the summary odds ratio for all-cause discontinuation as the authors did not report sufficient data in their paper to compute efficacy estimates."

Seven of the other nine studies are not mentioned at all, even in the 13 page "Full Texts Excluded" section of the Supplementary Material (pp. 32–44). The final two studies (Freeman et al., 1978; Johnstone et al., 1980), both published in the *Lancet*, are categorized as "Cannot be obtained" (Supplementary Material, p. 39). The personal communication did not answer the question "Does the Institute of Psychiatry not have access to papers published in the Lancet?" but did state that if they had managed to obtain these two papers (which JR had by now sent to them) neither would have met their inclusion criteria. The personal communication said the same of the seven studies which their paper failed to mention at all, but which they had also subsequently been sent by JR. For example, the Mutz et al. (2019) meta-analysis is the only one not to include the Lambourn and Gill study. The personal communication explained: "This trial was excluded as it did not meet our inclusion criteria of RDC, DSM or ICD diagnosis of major depressive disorder or bipolar depression."

So even after being sent all the studies which their search had missed, or they could not obtain, the *Institute of Psychiatry* reviewers conclude that after 80 years only one ECT–SECT study is robust enough to merit inclusion in meta-analyses.

*Quality Control*. The meta-analysis by Mutz et al. (2019) is the only one to report any sort of quality ratings for specific studies. Using Cochrane criteria they assess the only study they consider robust, in terms of their inclusion criteria, as having a "high risk" of bias, the worst Cochrane category.

*Short-term Findings*. Mutz et al. (2019) claim that their "network meta-analysis" produce odds ratios, relative to sham treatment, significantly in favor of ECT for "Bitemporal ECT" (bilateral) and "High-dose Unilateral ECT," but that the odds ratios for "Bifrontal ECT" and "Low to Moderate-Dose Unilateral ECT" are not significant. But the single ECT–SECT study they included only studied bilateral ECT, so conclusions about whether the other three electrode placements were superior to SECT were based on no ECT–SECT data at all. The personal communication explained:

> In the absence of head-to-head clinical trials, network meta-analysis allows us to estimate such treatment effects using data available from other treatment comparisons that share comparison treatments. For example, if we have data on treatment A vs treatment B and data on treatment A vs treatment C, we can estimate the effect of treatment B vs C. Please note that this is a somewhat simplified explanation.

In response to being asked why their review methodology led to an odds ratio for bilateral ECT far higher than the odds ratio calculated by the Pagnin et al. (2004) meta-analysis for the Brandon study, the reviewers replied: "The network meta-analytic ORs are not directly comparable to the individual study OR presented in the Pagnin et al. (2004) meta-analysis." This is very true. The OR calculated by Pagnin et al. (2004), based directly and solely on the ECT–SECT data of the Brandon study was 2.2. The OR calculated by Mutz et al. (2019), based on the Brandon data plus a lot of studies which do *not* compare bilateral ECT and SECT, is an enormous 8.9. Furthermore, their very large 7.3 OR for High-dose Unilateral ECT, is based *entirely* on studies that do not compare ECT and SECT.

We have already noted that the only ECT–SECT efficacy study that met their inclusion criteria was rated, by the reviewers themselves, as "high risk" of bias (Mutz et al., 2019, Supplementary Material, pp. 49, 50). They add:

> Overall risk of bias was deemed high in 19 trials (17%). In a sensitivity analysis excluding these trials, we found that . . . treatment effects of ECT protocols and magnetic seizure therapy versus sham therapy could not be estimated. (Mutz et al., 2019, p 10).

Nevertheless, they ignore their own statement, and proceed to estimate and report the treatment effects, unqualified, in the Abstract:

> 10 out of 18 treatment strategies were associated with higher response compared with sham therapy: bitemporal ECT (summary odds ratio 8.91, 95% confidence interval 2.57 to 30.91), high dose right unilateral ECT (7.27, 1.90 to 27.78). (Mutz et al., 2019, p.1)

*Follow-up Findings*. The reviewers make no attempt to review the literature regarding longer-term effects of ECT.

## DISCUSSION

### The Quality of the 11 Studies

Table 3 shows that the 11 studies produced Quality scores, on our 24-point scale, ranging from 9 to 17, with a mean score of 12.27 (*sd* = 3.20). Only three produced scores above 13.

The empirical support for using ECT prior to 1978 had consisted of just five ECT versus SECT studies, on a total of 67 ECT patients and 57 SECT controls, with a mean Quality score of 9.80 out of 24. Four of the five had found no difference between ECT and SECT. The only one finding a significant difference (Wilson et al., 1963) involved just four ECT patients.

The quality of this body of literature as a whole is unimpressive, and is clearly unable to determine whether ECT is more, or less, effective than SECT in reducing depression. Table 3 shows, for example, that 5 of the 11 studies (including three of the second wave) failed to describe their randomization process. Five (including two later studies) reported no attempt to test their blinding process. Of the six that did so, five assessed the blindness of the raters but not that of the patients; mostly by asking raters to guess whether patients had received ECT or SECT and finding no more agreement than that expected by chance (Brandon et al., 1984; Freeman et al., 1978; Johnstone et al., 1980; Lambourn & Gill, 1978), and in one instance by just reporting that it was "easy" for the observers to infer which treatment had been allocated (Fahy et al., 1963). The sixth study (Brill et al., 1959) tested the patients but not the raters, reporting that "some patients in the nonshock group believed that they were receiving some new variation of ECT." So none of the studies tested the blinding process for both the raters and the patients.

The second reason that none of the studies can reasonably claim to be double-blind is that none of them excluded people who had previously had ECT, so some members of the SECT groups would probably know they had not had ECT because they would know that ECT is always followed by headaches and temporary confusion. None of the studies

showed any awareness of this issue. Five of the 11 did not even report how many people had previously had ECT (see Table 3). Table 2 shoes that the other six reported percentages ranging from 21% (Johnstone et al., 1980) to 66% (Lambourn & Gill, 1978), with a weighted mean of 45.1% (the "nearly half" reported by Brill et al. (1959) was interpreted to be 14/30; 47%). So about half the patients in the SECT groups would probably have guessed that they had not had ECT. Therefore, none of the studies could genuinely be described as double-blind.

Two-thirds of ECT recipients are women and the average age is between 60 and 65 (Read & Bentall, 2010; Read et al., 2013, 2018); so the modal ECT person is a woman in her early sixties. Tables 2 and 3 show, however, that only three studies met the criterion of being broadly representative of the demographics of ECT recipients by using samples that were mostly female and had an average age of at least 50. None of the studies showed any interest in age or gender. None analyzed their findings by age or gender. None even reported ethnicity.

ECT is supposed to be given to severely depressed patients. Current guidance from the UK's National Institute for Health and Care Excellence states: "Consider ECT for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed. Do not use ECT routinely for people with moderate depression . . ." (National Institute of Clinical and Health Excellence [NICE], 2009). Five studies, however, failed to demonstrated that their participants were severely depressed; three did not provide enough information to know, and two clearly had only (Fahy et al., 1963) or mostly (West, 1981) moderately depressed participants. One used participants (62%) without a depression diagnosis at all (Ulett et al., 1956).

Two of the 11 studies invalidated their findings by administering ECT to the SECT group part way through the studies (Freeman et al., 1978; Harris & Robin, 1960). Table 3 reports that only five studies reported means and standard deviations on a dimensional depression scale such as the Hamilton, which is valuable for calculating an effect size and thereby making a meaningful contribution to a meta-analysis.

Only one of the studies reported whether other treatments (e.g., antidepressants or CBT) had been unsuccessfully tried prior to ECT, which would have rendered the studies able to assess whether ECT is effective for people who are today recommended for ECT by NICE guidelines (see above). In the only study that did report, less than half (46%) had been tried on antidepressants prior to the study (Freeman et al., 1978).

Only four studies included ratings by the patients themselves, and none assessed the impact of ECT, positive or negative, on their Quality of Life.

The sample sizes were small, ranging (ECT and SECT groups combined) from eight (Harris & Robin, 1960) and 10 (Wilson et al., 1963) to 77 (Brandon et al., 1984). The mean was 38.3; with 20.4 in the ECT groups, and 17.9 in the SECT groups.

Five studies selectively reported their outcomes, failing to report one or more findings.

## The Quality of the Five Meta-Analyses

All five of the meta-analyses claim that ECT is effective for depression but, as we have seen, they are all of a poor standard, not least because none of them pay sufficient attention to the quality of the papers on which they base this claim. The only meta-analysis conducted in the last 15 years, the one from the *Institute of Psychiatry* in London in 2019, is particularly

problematic. Mutz et al. (2019) make strong claims about the efficacy of ECT on the basis of just one ECT–SECT study (Brandon et al., 1984). They not only rated, themselves, that one study as having a "high risk" of bias by Cochrane criteria but stated that exclusion of high risk studies made it impossible to estimate an odds ratio for ECT. Furthermore 67% of the other studies (not ECT–SECT) in their network analysis, used to indirectly calculate odds ratios were, themselves, either "unclear risk" or "high risk" (Mutz et al., 2019, p. 6). As was the case for the other four meta-analyses, major flaws have to be ignored to claim that ECT is more effective than SECT.

Four of the five meta-analyses fail to report the quality of any of the studies they include, most of which are of a very poor standard. The exception is the recent *Institute of Psychiatry* meta-analysis, which, as we have seen, reports that the only study they include had an overall "high risk" of bias. It is worth noting that the study (Brandon et al., 1984) that Mutz et al. (2019) assessed as having a "high risk" of bias is the 3rd most rigorous study of the 11 studies according to our own Quality scale, suggesting that the other eight may be at least as equally problematic.

Given the overall low quality of the 11 studies it would be particularly important that only the best studies are included in meta-analyses. The authors' apparent disinterest in the fact that none of the studies were actually double-blind, in whether the participants were representative of who receives ECT in clinical practice, in whether ECT has any advantage over SECT beyond the end of treatment, and in the pervasive selective reporting, are all indicative of carelessness, bias, or both.

## Short-term Efficacy

Contrary to the claims by the authors of all five meta-analyses, the small number of studies, the small samples and the plethora of fundamental methodological flaws of most of the studies, render it impossible to determine whether or not ECT is superior to SECT during the treatment period,. The only three studies scoring 16/24 or higher on the Quality scale produced the following outcomes:

- Brandon et al. (16/24)—significant difference on psychiatrists' ratings, but patients' ratings not reported;
- Johnstone et al. (17/24)—no difference on nurses' ratings, no difference on patients' ratings; significant difference on psychiatrists' ratings (but for only two of three types of depression);
- Lambourn and Gill (17/24)—no difference on Hamilton scores or on psychiatrists' ratings.

This amounts to one of seven sets of ratings being significant and one partially significant.

While most of the 11 studies should never have been included in meta-analyses, it seems desirable to perform a meta-analysis on these three relatively high quality studies (keeping in mind that Mutz et al. (2019) evaluated the Brandon et al. (1984) study as "high risk" of bias). However, this is impossible because all three are guilty of selective reporting. One (Johnstone et al., 1980) failed to provide any data for two of their findings (both were merely reported as nonsignificant) and another (Brandon et al., 1984) failed to report anything at all about one of its two outcome measures (patients' self-ratings). The only

good-quality study to fully report its short-term findings (Lambourn & Gill, 1978) found no difference between ECT and SECT on either of its two measures.

### Long-term Efficacy

For the same reasons (but with even fewer studies) it is impossible to know whether or not ECT has any benefits, in terms of depression reduction, beyond the time of the last shock treatment. None of the three studies producing meaningful data found a significant difference. The best two studies found a near-zero effect size toward ECT of .065 (Johnstone, 1999) and a "small" (.299) effect size in favor of SECT (Lambourn & Gill, 1978). So it could be tentatively concluded that there really is no benefit beyond the end of treatment. To do so, however, on the basis of just two or three small studies, would be wrong. The truth is, as is the case for the short term, we don't know.

### Severely Depressed / Suicidal / "Treatment Nonresponders"

Even if one were to throw methodological caution to the wind, as the meta-analyses have done, and conclude that taken together there is some evidence that for the participants in the 11 studies there is, in general, an ECT–SECT short-term difference, this could definitely not be said to be true for the people who are supposed to receive ECT today—severely depressed, suicidal patients for whom other treatments have failed (NICE, 2009). Only six of the studies definitely included only or mostly severely depressed people. Two clearly did not. Although suicidal patients would probably have been included by chance in some studies, only two reported whether suicidal patients were actually included. The first actively excluded them (Fahy et al., 1963). In the second, only four of 31 (13%) people starting the trial had previously tried to kill themselves; and three of these four were withdrawn from the study (Harris & Robin, 1960).

We do not know, either, whether ECT is effective for people who have not responded to antidepressants or psychological therapies, the other major criterion for ECT use today, as we do not know how many, if any, such people were studied.

### Suicide Prevention

Government and professional guidelines have claimed, for decades, that ECT prevents suicide. Suicidality is said to be a key indicator of suitability for ECT. None of the meta-analyses report any findings that ECT is more effective than SECT at preventing suicide. There are none (Read & Arnold, 2017; Read & Bentall, 2010; Read et al., 2013). Although the Hamilton, MADRAS, and Beck depression scales all include questions about suicidal intent, only one study reported these specific outcomes. Lambourn and Gill (1978) found mean reductions on the suicide item of the Hamilton scale of 3.38 points in the ECT group and 3.32 in the SECT group.

The UK ECT Review Group states: "Although ECT is sometimes thought to be a life-saving treatment, there is no direct evidence that ECT prevents suicide" (p. 806). The 170-page UK government report states: "The evidence did not allow any firm conclusions to be drawn regarding the . . . impact of ECT on all-cause mortality." (Greenhalgh et al., 2005, p. X).

### Quality of Life

Quality of life measures can provide a more comprehensive and holistic assessment of our well-being than a depression scale; and one's quality of life can influence one's mood. None of the studies attempted to determine whether ECT improves quality of life, a failing noted by Greenhalgh et al. (2005, p. 15).

### Patients' Experience

Only five studies included (and only four reported) any measure completed by the patients themselves. We agree with Kingsley and Patel (2017) that patient-reported outcome measures should be included in clinical trials and meta-analyses of psychiatric conditions. In one of the four studies that did report the patients' assessments of change, the psychiatrists reported a significant difference between ECT and SECT and the patients did not (Johnstone et al., 1980). In another study both the psychiatrists' ratings produced a significant difference but only one of the two self-rated scales did so (Freeman et al., 1978).

### Gender

Women are twice as likely to receive ECT as men (Leiknes et al., 2012; Read et al., 2013, 2018). Yet none of the 11 studies or meta-analyses reported whether ECT was more or less effective for this group. Seven of the eight mixed gender studies failed to report data by gender. The two all-female studies produced one positive (Wilson et al., 1963) and one negative finding (Harris & Robin, 1960)—both with tiny samples.

The only study to report data for individuals by gender (Lambourn & Gill, 1978) allows us to calculate that the nine women who received ECT had a mean reduction on the Hamilton of 30.0 points, while the nine in the SECT group had a mean reduction of 18.6, a difference of 11.4 in favor of ECT. The men, however, had mean reductions of 21.4 points with ECT and 27.4 points with SECT, a difference of 6.0 points in favor of SECT. This suggests that ECT may be initially effective for women, but not for men. However, at 1 month follow-up (excluding those who received ECT after the end of treatment) the four women in the SECT group had a mean improvement of 4.0 points greater than the four women in the ECT group, while the four men in the SECT group had a mean improvement of 9.7 points greater than the three men in the ECT group. (This study, like Johnstone et al. (1980), used only one rater for Hamilton scores, and apparently doubled the scores of that person.)

Thus, there is only scant evidence that ECT might be effective in the short-term for one of its major target groups—depressed women; and none that it is effective beyond the end of treatment for them. The 170-page report conducted for the UK's National Health Service concluded "The evidence did not allow any firm conclusions to be drawn regarding the efficacy of ECT in . . . women with psychiatric problems" (Greenhalgh et al., 2005, p. X).

### Age

The average age of ECT recipients is usually between 60 and 65 (Leiknes et al., 2012; Read et al., 2013, 2018). One would assume that studies and meta-analyses would therefore pay particular attention to older people. However, with the exception of the smallest study

(Harris & Robin, 1960), the average age of the samples ranged from 35 to 54, and some had no patients at all over 60, or 65 (see Table 1). No analyses by age were conducted by any of the studies.

One study did report individuals' ages and outcomes (Lambourn & Gill, 1978). The six people aged 60 or older who received ECT had a mean fall in Hamilton scores of 16.7, while the 10 aged under 60 had nearly double the improvement (32.0), a large, but non-significant, difference ($t$ (14) = 1.77, $p$ = .09). Improvement in the under 60s was, on average, 10.3 points greater in the ECT group than in the SECT group. In the 60 or over group improvement was an average of 8.7 points greater in the SECT group than the ECT group. Six of the 10 under 60s, but none of the 60 or older group, scored a 3 on the 0–3 doctors' scale, a significant difference ($\chi^2$ = 5.76, $p$ = .016).

One meta-analysis (Kho et al., 2003) found no difference between patients over and under 65 (p. 143; based on 15 ECT samples in studies *without* SECT groups). An additional meta-analysis, a Cochrane review, reported specifically on the effectiveness of ECT for the "depressed elderly" (van der Wurff et al., 2003). It identified only one study comparing ECT and SECT (O'Leary et al., 1994). This was a re-analysis of data for the 35 people aged over 60 in the Gregory et al. (1985) study. Twelve of the 35 had been withdrawn before completion of the study and the reviewers identified additional "major methodological shortcomings" before deciding that "None of the objectives of this review could be adequately tested because of the lack of firm, randomised evidence" (p. 2).

The UK ECT Review Group similarly concluded:

> Despite the reputation of ECT for efficacy in older patients, elderly people tend to be under-represented in trials, which limits the confidence with which results can be used to lend support to clinical practice in this subgroup. (p. 806)

Greenhalgh et al. (2005) concurred, with: "There was no randomised evidence of the efficacy of ECT in people older than 65 years" (p. 45) and "The evidence did not allow any firm conclusions to be drawn regarding the efficacy of ECT in older people." (p. 81)

Thus, there is no evidence that ECT is effective for another of its major target groups —the depressed elderly, either in the short or longer term. Use with this group is especially problematic because it is well established that older people are particularly likely to develop memory loss as a result of ECT (Mosti & Brook, 2019; Sackeim et al., 2007).

## Children or Adolescents

No children or adolescents were included in any of the studies. There is no placebo-controlled evidence that ECT is, or is not, effective for these groups, either in the short or longer term.

## Involuntary Patients

Many ECT recipients are given it against their will; about 40% in England (Read et al., 2018). None of the studies or meta-analyses addressed the issue of whether the trauma of being forced to undergo ECT after stating that you do not want it reduces the probability of a positive outcome. The UK government's report noted that even what they considered to

be the best of the meta-analyses (UK ECT Review Group, 2003) "did not identify any trials that explored . . . the impact of consumer choice on the outcomes of ECT" (Greenhalgh et al., 2005, p. 15)

Six of the 11 studies made no mention of whether some participants were being coerced to have ECT against their will, or even whether participants gave consent to take part in the study (Brill et al., 1959; Fahy et al., 1963; Freeman et al., 1978; Harris & Robin, 1960; Ulett et al., 1956; Wilson et al., 1963). These studies included most or all patients given ECT in a particular hospital and therefore almost certainly included some patients detained under mental health legislation and/or given ECT against their will. Wilson et al. (1963) refer to the withdrawal of "a voluntary patient signed out by husband" implying that some participants were involuntary. Two studies reported that participants gave consent for the study but made no mention of whether some participants were being coerced to have ECT (Lambourn & Gill, 1978; West, 1981). Three studies explicitly excluded people who were being treated under the Mental Health Act or were been given ECT against their expressed wish (Brandon et al., 1984; Gregory et al., 1985; Johnstone et al., 1980).

Only one of the five studies that found no difference between ECT and SECT, therefore, had excluded people who were having ECT against their will, but the three studies that did make this an exclusion criterion produced positive findings. Thus, it is possible that ECT is even less effective under compulsion than when undertaken voluntarily. This makes intuitive sense, but the evidence is weak. It is all we have to go on, as none of the studies that did include coerced patients analyzed their outcomes separately; and those later studies that (for sound ethical reasons) excluded coerced patients could not answer the question.

What can safely be concluded is that there is no evidence that ECT is effective for coerced patients, either in the short or longer term. This is perhaps the most alarming of all our specific findings. To administer a treatment involving multiple use of general anaesthesia, multiple electric shocks and multiple grand mal convulsions, against someone's will, is unethical. To do so even in the absence of any evidence that there is a good chance of a positive outcome is especially alarming. We have no idea whether this treatment works under compulsion. To do so, therefore, is clearly both unscientific and unethical.

### Unilateral versus Bilateral

The purpose of the current review is to determine whether the meta-analyses were correct to claim that ECT is, in general, more effective than SECT, not to compare different types of ECT. We should nevertheless report that only two of the 11 studies used unilateral electrode placements. All the participants in the Lambourn and Gill were administered unilateral ECT, which produced the same outcomes as SECT at the end of treatment and worse outcomes than SECT at follow-up. In the Gregory et al. (1985) study both unilateral and bilateral placement produced significantly better outcomes than SECT at the end of treatment, but no meaningful follow-up occurred. Therefore, the millions of administrations of unilateral ECT over the past 35 years (Leiknes et al., 2012), since the 1985 Gregory et al. (1985) study, have been based on one positive and one negative finding in the short term and one negative finding at follow-up.

### Placebo

Hope is a powerful placebo factor in psychiatric treatments, biological or psychological. It effects doctors, nurses, patients, and their loved ones. It can influence not just perceptions

of recovery but actual recovery. In the 1940s psychiatrists were excited about the new treatment. Hope of recovery had returned to some of the most depressing of institutions. Neurologist John Friedberg suggested that in those early days "the influence of ECT was on the minds of the psychiatrists, producing optimism and earlier discharges" (Friedberg, 1976).

Almost all the 11 SECT studies found that having a series of general anaesthetic procedures in the belief that you are having a major medical procedure that the doctors and nurses believe in can temporarily improve mood. Some of the researchers commented on this:

> One possibility is that the effective therapeutic component of ECT is the repeated rapid induction of unconsciousness in the patient. . . . It could very well be that the primary therapeutic agent is the psychological meaning of the treatment to the patient. . . . The influence of the unusual amount of care and attention which all receive could be studied further. (Brill et al., 1959, p. 633).

> Effectiveness . . . is due in large part to the attendant procedures associated with, the administration of an anaesthetic and the mystique associated with an unusual form of treatment. (Lambourn & Gill, 1978, p. 519).

> The results confirm that many depressive illnesses although severe may have a favourable outcome with intensive nursing and medical care even if physical treatments are not given. (Johnstone et al., 1980, p. 1319)

Brandon et al. (1984, p. 23) noted that an early version of convulsive therapy had been abandoned because it was no better than placebo:

> If the undoubted beneficial effects of electroconvulsive therapy were due to an elaborate placebo response the treatment would be comparable with insulin coma therapy, in which Ackner et al. had shown that any effects were not due to the induction of coma with insulin. The absence of a specific antidepressant effect would provide a strong case for abandoning electroconvulsive treatment.

A review focussing just on the placebo response with ECT (Rasmussen, 2009) found "an unexpectedly high rate of response in the sham groups" and concluded "The modern ECT practitioner should be aware that placebo effects are commonly at play" (p. 59). Furthermore:

> It is recognized that through a complex set of circumstances related to the meaning a patient ascribes to encounters with health care providers, which are influenced by cultural factors, individual life experiences, education, and the manner in which doctors communicate, expectations develop in the mind of the patient which by themselves can result in measured improvement in the condition at hand. . . . Finally, one also should not discount the effect of the natural history of depressive episodes. In none of the studies was there an untreated, natural history control group. Patients tend to get better on their own, even without treatment. (p. 58)

Lambourn and Gill reiterated that last, crucially important but often ignored, point:

> The contribution of spontaneous remission during this study remains an unknown factor because of the lack of a totally untreated group. (p. 515)