ELECTROCONVULSIVE THERAPY:
WHAT YOU NEED TO KNOW

An Information Booklet for Patients and Families

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What is Electroconvulsive Therapy?

Electroconvulsive therapy (ECT; called "shock treatment" by some) is a safe and effective medical treatment for certain psychiatric disorders. During this treatment, a small amount of electricity is applied to the scalp which produces a seizure in the brain. The procedure is painless because the patient is asleep, under general anesthesia. At the time of the treatment, medication is also used to reduce the bodily movements that would ordinarily occur during a seizure.

Who is Treated with ECT?

ECT has been used continuously for over 80 years. In the United States, about 100,000 individuals are estimated to receive ECT each year, and more than 1,000,000 people annually may receive this treatment world-wide.

In 2018, the US Food and Drug Administration (FDA) determined that special controls, identified in a final order issued on December 26, 2018, along with general controls, were sufficient to provide a "reasonable assurance of safety and effectiveness for the use of ECT in treating catatonia or a severe major depressive episode (MDE) associated with major depressive disorder (MDD) or bipolar disorder (BPD) in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition."

Aside from psychiatric diagnosis, other considerations determine whether or not ECT is an appropriate treatment. Most commonly, ECT is given when patients are "treatment resistant" and have not benefited sufficiently from other treatments. Additionally, ECT may be recommended when it is particularly important that patients recover quickly and fully due to severe and perhaps life-threatening psychiatric or medical conditions.

Precaution

Historically, patients with diagnoses other than MDE and catatonia have frequently been treated with ECT. However, the safety and effectiveness of ECT for the treatment of patients with schizophrenia, schizophreniform disorder, schizoaffective disorder, and bipolar mania or mixed states has not been established. In the FDA December 26, 2018 final order, the FDA determined that the special controls identified in the final order, along with general controls, were sufficient to provide a reasonable assurance of the safety and effectiveness of ECT for use in treating catatonia or a severe major

depressive episode (MDE) associated with major depressive disorder (MDD) or bipolar disorder (BPD) in patients age 13 years and older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. The use of ECT in other conditions is considered "off-label" use.

Why Hasn't ECT been Replaced by Medications or Psychotherapy?

The alternatives to treatment with ECT include psychotherapy (talk therapy), medication therapy, and other forms of brain stimulation, such as transcranial magnetic stimulation (TMS). Whether ECT is the appropriate treatment depends on the patient's history of response to other treatments, the urgency that dictates that fast and extensive improvement be obtained due to the severity of the psychiatric or medical condition, the history, if any, of previous response to ECT, and the patient's preference. When considering ECT, it is important to discuss these issues with treatment providers.

Not all patients improve when treated with medications or psychotherapy. Indeed, it is estimated that about one-third of patients with a major depressive episode (MDE) are "treatment resistant" as they have not substantially benefited from at least two adequate trials of antidepressant treatment (Rush et al., 2006, Thase, 2011, Sackeim et al., 2019). ECT has been shown repeatedly to be effective in many individuals with treatment-resistant depression.

Some depressed patients have severe and potentially life-threatening psychiatric problems, such as suicidal inclinations, psychotic (delusional) thinking, or stupor. Similarly, catatonia is often a life-threatening condition, especially in patients who have not benefited from first-line medication (benzodiazepine) treatment. ECT is often recommended when it is critical to obtain rapid improvement due to these conditions.

How is ECT Given?

ECT may be given on an inpatient or outpatient basis, depending on the patient's medical condition and circumstances, and the facility where they are treated. ECT is always administered by a treatment team. The team usually consists of a psychiatrist, an anesthesiologist or other anesthetist, and a nurse.

Before ECT is started, the patient undergoes psychiatric and medical evaluations. This often includes a medical history, physical examination, electrocardiogram (EKG) and other tests, as needed. The medications the patient is receiving may have to be adjusted.

ECT treatments are usually given at spaced intervals, twice or three times per week. The most common schedule in the US is three times per week – in the morning on Monday, Wednesday and Friday. Before each treatment, patients are instructed not to eat or drink for a specified period of time. Patients should also try to refrain from smoking during the morning prior to the treatment. If being treated as an outpatient, the patient should be accompanied home after the treatment.

When the patient comes to the ECT treatment area, an intravenous line is started. Sensors for recording EEG (electroencephalogram, a measure of brain activity) are placed on the head. Other sensors are placed on the chest for monitoring ECG (electrocardiogram, measuring heart rate and rhythm). A cuff is wrapped around an arm for measuring blood pressure. The areas on the scalp where the ECT electrodes will be placed are cleansed and prepared for the treatment. When everything is connected and in order, a sleeping medication (e.g., methohexital, propofol, thiopental, ketamine, or etomidate) is injected through the intravenous line. This medication will cause the patient to sleep for 5 to 10 minutes. Once the patient falls asleep, a muscle relaxant (succinylcholine) is injected. The muscle relaxant prevents movement of the body, and during the seizure there are only minimal contractions of the muscles.

When the patient is completely asleep and the muscles are well relaxed, the treatment is given. A brief electrical stimulus is applied to electrodes on the scalp. The current passes through the scalp and skull and stimulates the brain, resulting in a generalized seizure that lasts for about a minute. If you were watching the procedure, you might notice that the toes wiggle, but little else. The occurrence of the seizure in the brain and its termination are confirmed by inspection of the EEG recording.

Throughout the procedure, the patient receives oxygen through a mask. This continues until the patient resumes breathing on his or her own, which typically occurs within a few minutes of the end of the seizure. When the treatment is

completed, the patient is taken a recovery area for further monitoring by trained staff. Usually within 30 to 60 minutes, the patient can leave the recovery area.

How Many Treatments are Needed?

ECT is given as a series of treatments. The total number needed to successfully treat psychiatric disturbance varies from patient to patient. For MDE, the typical range is from 6 to 12 treatments, but some patients may require fewer and some patients may require more treatments to achieve maximal benefit. In some patients with catatonia, profound improvement is observed after a single treatment, although, again, other patients may show slower improvement.

Is ECT Curative?

ECT is highly effective in providing short-term relief from psychiatric symptoms. However, permanent cures for psychiatric illness are rare, regardless of the treatment given.

If ECT is not followed by adequate continuation treatment, the rates of relapse are high. To prevent relapse following ECT, virtually all patients require further treatment with medications and/or ECT. There is substantial evidence that specific medication strategies and/or use of ECT as a continuation treatment are effective for many individuals in preventing relapse. Nonetheless, it should be noted that following successful ECT, even with optimal continuation treatment, some patients relapse and may require additional acute courses of ECT to achieve symptom relief.

If ECT is used as part of the treatment strategy to protect against relapse, it is usually administered to outpatients on a weekly to monthly basis, often with concomitant psychiatric medications. However, the extended use of ECT (more than 3 months of treatment) for the purpose of relapse prevention is considered “off-label” use.

The patient should be warned: “Warning: When used as intended this device provides short-term relief of symptoms. The long-term safety and effectiveness of ECT treatment has not been demonstrated.”

How Safe is ECT and What are its Physical Risks?

The physical risks of ECT may include the following (in order of frequency of occurrence):

i. Pain/somatic discomfort (including headache, muscle soreness, and nausea);

ii. Skin burns;

iii. Physical trauma (including fractures, contusions, injury from falls, dental and oral injury);

iv. Prolonged or delayed onset seizures;

v. Pulmonary complications (hypoxemia, hypoventilation, aspiration, upper-airway obstruction);

vi. Cardiovascular complications (cardiac arrhythmias, heart attack, high or low blood pressure, and stroke); and

vii. Death.

Like other medical treatments, ECT has risks and side effects. As with any procedure involving general anesthesia, there is a possibility of death. Death associated with ECT is rare, but the risk is higher in patients with severe medical conditions.

ECT can result in a number of serious medical complications, but the overall rate of such complications is low. Serious medical complications include cardiovascular events such as heart attack or stroke. These complications are rare. More frequently, ECT can result in hypertension, hypotension, or irregularities in heart rate or rhythm, especially at the time of the treatment. These cardiovascular abnormalities are usually transient or easily managed with medications. However, in rare instances these complications may also be life threatening.

ECT can result in pulmonary complications. These adverse events may involve insufficient oxygen in the blood or tissue (hypoxia), respiratory depression, aspiration, or airway obstruction. Some pre-existing medical conditions increase the risk of cardiovascular or pulmonary complications and should be identified and discussed in the pre-ECT medical evaluation. The

medical management of these pre-existing conditions may need to be optimized to reduce the likelihood of a serious complication during ECT.

ECT involves the deliberate production of a self-terminating, generalized seizure in the brain. It is widely thought that the seizure is key to the therapeutic effects of the treatment. While the typical ECT-induced seizure spontaneously terminates after about a minute, in some patients the seizure may last longer. When seizures persist for longer than 2-3 minutes, they are defined as prolonged. Were this to happen, the responsible physicians will stop the seizure by administering an anticonvulsant medication through the intravenous line. In contrast, delayed onset or tardive seizures are rare events in which the patient has a spontaneous seizure sometime after the ECT-induced seizure terminated. The occurrence of such a rare event will trigger evaluation of medications and/or neurological conditions that contribute to this delayed seizure activity.

Before the routine use of anesthesia and muscle relaxation as part of the ECT procedure, skeletal injuries, including fractures, were common. In contemporary practice, physical trauma injuries are potentially possible, but rare. Such trauma may include fractures, contusions, injury from falls, and dental and oral injury. With modern anesthesia techniques, dental complications are infrequent and bone fractures or dislocations are rare. In addition, use of a “bite block” is routine and substantially reduces the risks of injury by protecting the dental and oral structures.

The ECT device passes a small current between in the two electrodes. In order to keep the current at the prescribed intensity, the ECT device adjusts the voltage as a function of the electrical resistance (impediments to the flow of electricity) in the circuit. Theoretically, a high degree of resistance could result in use of high voltage, resulting in skin burns on the scalp, in the area under the ECT electrodes. However, modern ECT devices reduce this risk by placing a cap on the maximal voltage that can be administered, and in some cases, by automatically terminating electrical stimulation if the resistance is too high. Nonetheless skin burns have occurred during the administration of ECT.

The complications discussed above (cardiovascular, pulmonary, prolonged and tardive seizures, physical trauma [fracture and dental injury], and skin burn) can be considered as serious adverse medical events depending on

their severity, outcome and impact on subsequent care. Whether ECT is appropriate for any patient involves consideration of the likely and potential benefits and risks of ECT relative to those of alternative treatments.

The most common side effects of ECT involve pain or other somatic disturbance, and include headache, muscle soreness, and nausea. Headache is common and most frequently reported immediately following the treatment. Muscle soreness is usually due to the muscle movements (fasciculations) produced by the muscle relaxant medication (succinylcholine) and is often experienced only at the first few treatments. Other physical side effects include nausea, which may last for a few hours. These relatively common side effects typically respond to simple treatments.

Can ECT Worsen Psychiatric Conditions?

In addition to serious medical complications, there is the possibility of worsening of psychiatric symptoms. Not all patients have improvement of symptoms following ECT, and depressive or catatonic symptoms may worsen.

Warning: Patients treated with ECT may experience manic symptoms (including euphoria and/or irritability, impulsivity, racing thoughts, distractibility, grandiosity, increased activity, talkativeness, and decreased need for sleep) or a worsening of the psychiatric symptoms they are being treated for.

In patients with bipolar disorder, ECT may induce a switch from a major depressive episode (MDE) into a mixed state (both depressive and manic symptoms), hypomania, or mania. Manic symptoms include euphoria and/or irritability, impulsivity, racing thoughts, distractibility, grandiosity, increased activity, talkativeness, and decreased need for sleep. All antidepressant treatments may potentially induce such switching, and ECT may be less likely to do so than some antidepressant medications (Devanand et al., 1988b, Devanand et al., 1992). Nonetheless, a switch into a mixed, hypomanic, or manic state is possible.

What are Effects of ECT on Thinking and Memory?

On awakening following the treatment, patients will experience some confusion (disorientation). This is partly due to the anesthesia and partly due to the treatment. During this period of disorientation, the patient may be confused

about basic information, such as the day of the week, their own age, or where they are. With modern ECT techniques, the confusion typically clears within an hour, and often within 15 minutes or sooner. The confusion or disorientation seen directly after the treatment is short-lived and fully reversible.

As a result of their severe psychiatric illness, many individuals come to ECT with impairments in concentration, attention, and other cognitive abilities. The psychic turmoil produced by these disorders interferes with fundamental cognitive functions, such as the capacity to attend to what others are saying or to be free from distraction and concentrate on a task. Since these functions are critical to learning new information or carrying out complex instructions, many different cognitive capacities may be impaired. Consequently, when the psychiatric disturbance improves following ECT, there is often improvement in diverse aspects of thinking.

The side effect of ECT that has received the most attention is memory loss. ECT results in two types of memory loss. The first involves rapid forgetting of new information (anterograde amnesia). For example, shortly following the treatment, patients may have difficulty remembering conversations from earlier that day, things they have recently read, or a shopping list they put together a few hours before. This type of memory loss specifically involves difficulty in retaining newly learned information. This type of memory loss is short-lived and has not been shown to persist for more than a few weeks following the completion of ECT (Semkovska and McLoughlin, 2010).

The second type of memory loss concerns amnesia for events from the past (retrograde amnesia). Some patients will have gaps in their memory for events that occurred in the weeks to months and, less commonly, years prior to the treatment course. This memory problem also improves following the completion of ECT and tends to go away within a few days to a few months. However, in some patients, there may be permanent gaps in memory for events that occurred close in time to the treatment (Sackeim, 2014, Semkovska et al., 2016). As with any treatment, patients differ in the extent to which they experience side effects, and more extensive memory loss for past events can occur. This type of retrograde amnesia can pertain to information about the world (e.g., memory of public events) or information about one's own life (e.g., the overseas trip taken last year). When the amnesia pertains to one's life history, it is termed retrograde amnesia for autobiographical memory. Permanent autobiographical amnesia extending back for various periods of

time has been reported by some patients who have received ECT. Some patients find the autobiographical amnesia the most distressing aspect of this treatment.

All patients will experience some variable period of confusion and disorientation when awakening following each treatment. Retrograde amnesia, especially for autobiographical memory, is an established risk of the procedure. Consequently, the prospective patient should be warned: **"Warning: ECT device use may be associated with disorientation, confusion, and memory problems."**

Because of possible problems with confusion and memory, it is usually recommended that patients not make any important personal or business decisions during or immediately following the ECT course. During and shortly after the ECT course, and until discussed with the supervising physician, patients should refrain from driving, transacting business, or other activities for which memory difficulties may be troublesome.

Are There Different Forms of ECT?

The methods used to administer ECT have changed radically since its introduction over 80 years ago. Indeed, the period of confusion following each treatment and the extent of memory loss were far greater in earlier eras than with modern techniques. Nonetheless, ECT can be performed with techniques that differ in how the brain is stimulated.

In modern ECT, electrodes can be placed over different scalp regions. For example, with bilateral (bifrontotemporal) ECT electrodes are placed over the left and right temple areas. In contrast, with right unilateral ECT, both electrodes are placed on the right side of head, one over the temple area and the other near the midline. In general, the unilateral placement is associated with less confusion and memory effects than the bilateral placement. Some practitioners believe, however, that the bilateral placement is the most definitive treatment with respect to efficacy.

Another distinction concerns the electrical waveform used to stimulate the brain. Modern ECT devices deliver a series of rectangular pulses of specified duration and amplitude. The duration of the pulse may be "brief" (0.5-2.0 milliseconds) or "ultrabrief" (0.15-0.49 milliseconds).

Individuals differ considerably in the minimal overall amount of electricity (charge) needed to trigger the generalized seizure. Keeping the amount of electricity in the appropriate range relative to the individual patient's seizure threshold is considered a key feature in ensuring efficacy and minimizing adverse effects on thinking and memory. An excessive amount of electricity may exacerbate cognitive effects, while an insufficient amount may undermine efficacy. Different methods are in use for determining the amount of electricity for individual patients. These methods include basing the amount of electricity on patient age, basing it on a more complex predictive formula, or using an "empirical method" in which the seizure threshold is identified by progressively increasing the amount of electrical stimulation while under anesthesia.

How Does ECT Work?

Like many other treatments in medicine, the exact process that underlies the effectiveness of ECT is uncertain. It is known that the benefits of ECT depend on producing a seizure in the brain and on technical factors in how the seizure is produced. Specifically, the path of the current in brain tissue and the amount of current within that path are critical in determining the efficacy of the treatment.

A cascade of biological changes that result from the seizure may underlie effectiveness. The seizure terminates spontaneously because it triggers an active inhibitory process involving release of specific brain chemicals that stop seizure activity.

ECT also has consistent effects on a variety of other brain chemical systems, involving specific neurotransmitters, peptides, and hormones. ECT not only modulates the concentrations of many of these substances, but it modulates diverse aspects of neural transmission. Some of the changes in brain chemistry may underlie specific modes of action.

Appendix

Contraindications
Some medical conditions substantially increase the risks of ECT (American Psychiatric Association, 2001, Mankad et al., 2010, Weiss, 2018, Ferrier and Waite, 2019, Weiss et al., 2019). Administering ECT in the presence of such conditions can substantially increase the likelihood of significant morbidity and mortality. However, untreated or ineffectively treated psychiatric illness may also increase patient risks. Consequently, the American Psychiatric Association Task Force Report on ECT recommends that an assessment of the relative risks and benefits of ECT be conducted for each individual patient. This analysis should include evaluation of four elements: (1) the severity and duration of the psychiatric illness and its threat to life; (2) the likelihood of therapeutic benefit if the patient is treated with ECT; (3) the medical risks of ECT and the extent to which those risks can be mitigated or reduced; and (4) the likely benefits and risks of alternative treatments and of no treatment.

The cardiovascular, central nervous, and pulmonary systems are the source of the greatest risks of ECT. The type and severity medical co-morbidities are often predictive of the medical complications that arise during the treatment. For example, the type and severity of pre-existing cardiac disease is predictive of the likelihood, type, and severity of cardiac complications during ECT (Zielinski et al., 1993, Agelink et al., 1998, Luckhaus et al., 2008). For example, recent myocardial infarction increases the risk of reinfarction (Applegate, 1997).

Cardiovascular System. Severe and unstable cardiovascular conditions may substantially increase risks. These conditions include:

- Recent and/or severe myocardial infarction
- Unstable angina
- Uncompensated congestive heart failure
- Vascular aneurysm or stenosis
- Clinically significant arrhythmias
- Uncontrolled hypertension or hypotension

The application of electrical stimulus results in an immediate bradycardia and reduction in blood pressure, while the elicitation of the generalized seizure results in tachycardia and increased blood pressure (Prudic et al., 1987, Drop and Welch, 1989, Webb et al., 1990). In turn, these changes in cardiac function may trigger cardiovascular adverse events, including asystole, myocardial infarction, ischemia, ruptured aneurysm, and prolonged hypertension or hypotension. Modification of patient ongoing pharmacology and/or the medications administered at ECT may reduce the likelihood of significant morbidity and mortality (Stoudemire et al., 1990, Weinger et al., 1991, Dolinski and Zvara, 1997, Rayburn, 1997).

Central Nervous System. ECT results in a transient increase in intracranial pressure, associated with the large increase in cerebral blood flow and cerebral blood volume during the induced seizure (Meldrum and Nilsson, 1976, Ingvar, 1986, Takano et al., 2007). Thus, the medical risks of ECT are substantially elevated in patients with neurological disorders associated with increased intracranial pressure or other signs of a mass effect and in patients with focal cerebrovascular fragility. These conditions include:

- Space-occupying cerebral lesions, such as tumors or hematomas.
- Cerebrovascular aneurysms or malformations
- Recent stroke (hemorrhagic or ischemic)
- Other causes of increased intracranial pressure (e.g., hydrocephalus, meningitis, encephalitis)
- Skull defects (which may include metal devices in or near the site of stimulation). Metal devices, such as screws and plates or metal meshes, may preclude specific stimulation patterns but may not preclude treatment administration completely.
- Implanted active stimulatory devices (e.g., Deep Brain Stimulation devices). Stimulation devices may pose a risk to the patient if the flow of current during treatment damages active components of the device (i.e. potential for catastrophic failure of the battery).

Application of ECT in the context of already increased intracranial pressure or mass effect due to space-occupying lesions or other causes may result in seizures, stroke, neurological damage, and death. Similarly, application of ECT in patients with recent stroke or cerebral aneurysms or malformations may lead to additional cerebrovascular compromise, including bleeds, and acute neurological decompensation (Krystal and Coffey, 1997). Stimulation over a skull defect

may substantially alter the intracerebral distribution of current density and lead to diminished efficacy, excessive cognitive effects, and/or neurological damage (Everman et al., 1999, Kant et al., 1999, Wijeratne and Shome, 1999).

Pre-existing cognitive impairment due to neurological disorder, such as dementia, may increase the risk of acute cognitive worsening during and following the ECT course (Krystal and Coffey, 1997). Patients with myasthenia gravis or upper motor neuron disease (e.g., quadriplegia or amyotrophic lateral sclerosis) may have heightened sensitivity to the depolarizing muscle relaxant, succinylcholine, and may require dosage adjustment or use of a nondepolarizing agent (American Psychiatric Association, 2001).

Pulmonary System. Severe and unstable pulmonary conditions increase the risks of problematic airway management and aspiration during and immediately after ECT (Mueller et al., 2006, Schak et al., 2008, Blumberger et al., 2017). These conditions include:

- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Pneumonia

Problems in airway management during ECT may result in aspiration pneumonia, hypoxia, neurological damage, and death. To mitigate these risks it is widely recommended that patients with COPD continue treatment with bronchodilators throughout the ECT course and that they receive adequate preoxygenation at each treatment (Wingate and Hansen-Flaschen, 1997). It is noteworthy that theophylline, a medication commonly used to treat COPD, interferes with seizure termination and has been linked to prolonged seizures and status epilepticus (Devanand et al., 1988a, Rasmussen and Zorumski, 1993, Fink and Sackeim, 1998). Its use should be discontinued or minimized during the ECT course. Asthmatic patients should have bronchodilators available for use, if needed, before and following each treatment.

Other Conditions that Substantially Elevate Risk. Patients may present with other severe and/or unstable medical conditions that substantially increase the risks of ECT. Such patients are rated as level 4 or 5 on the American Society of Anesthesiologists physical status classification (Mayhew et al., 2019).

Summary of Clinical Outcomes and Adverse Events and Complications Associated with Use of the Device

spECTrum devices, the predecessor to SigmaStim Σigma devices, have been used in many of the prospective, randomized trials that have defined the clinical outcomes that occur with ECT, as well as its profile of adverse events and side effects. For example, spECTrum and earleir MECTA ECT devices were used in the systematic studies conducted at the New York State Psychiatric Institute/Columbia University and multiple collaborating institutions (Sackeim et al., 1987, Sackeim et al., 1993, McCall et al., 2000, Sackeim et al., 2000, Sackeim et al., 2008, Sackeim et al., 2009, Prudic et al., 2013, Sackeim et al., 2020). This research developed the stimulus dose titration method and established the effects of electrode placement, waveform, and stimulus dosing on efficacy, cognition and neurophysiological, cardiovascular, and endocrinological measures. This and other work has demonstrated that spECTrum devices are highly efficacious in the treatment of MDE, with notably high remission rates reported in these blinded trials. Presented in this section below are summaries of the procedures, findings, and conclusions of three exemplary randomized clinical trials that used the spECTrum device in the treatment of major depressive episode (Sackeim et al., 2008, Sackeim et al., 2009, Semkovska et al., 2016).

With respect to cognition, studies using intensive neuropsychological testing of patients treated with spECTrum devices have consistently observed that retrograde amnesia for autobiographical information is a persistent adverse cognitive effect of the treatment, and that the severity of this deficit is systematically related to treatment parameters (McElhiney et al., 1995, Sackeim et al., 2008, Sackeim, 2014, Semkovska et al., 2016). Much of what is known about the profile of adverse cognitive effects and how treatment technique impacts on their manifestation derives from use of MECTA devices.

There are no randomized trials that compare ECT devices in clinical outcome, adverse events or complications. However, the characterization of the beneficial and adverse effects of ECT in this manual, and by the field more generally, is substantially based on the evaluation of patients treated with MECTA devices.

MECTA tracked provider and patient/consumer reports of adverse events since the introduction of spECTrum devices. Few reports of any type have been received over the lifetime of these devices.

Sackeim et al. (2008): Effects of Pulse Width and Electrode Placement

Authors:	Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, Berman RM, Brakemeier EL, Perera T, Devanand DP.
Title:	Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy.
Major Publication:	Brain Stimulation. 2008;1:71-83.
Study site(s):	New York State Psychiatric Institute/Columbia University
Study protocol:	In a double-masked trial, 90 depressed patients were randomized to right unilateral (RUL) ECT at 6 times seizure threshold or bifrontotemporal (bilateral, BL) ECT at 2.5 times seizure threshold, using either a traditional brief pulse width (1.5 milliseconds) or an ultrabrief pulse width (0.3 millisecond). Depressive symptoms and cognition were assessed before and during the ECT course, and immediately, 2 months, and 6 months after ECT. Patients who responded were monitored for relapse for a 1-year period. Patients were withdrawn from all psychotropics medications before and during the ECT treatment period other than lorazepam (up to 3 mg/d). Patients, clinical outcome raters, and neuropsychology technicians were masked to treatment conditions. This trial tested the hypotheses that combining ultrabrief stimulation with the RUL electrode placement results in preserved ECT efficacy and a substantial reduction in acute, short-term and long-term adverse cognitive effects. It was also hypothesized that ultrabrief stimulation is more efficient than brief pulse stimulation in the charge needed for seizure induction (initial seizure threshold).
Patient population studied:	Patients met Research Diagnostic Criteria and Diagnostic and Statistical Manual IV (DSM-IV) criteria for major depressive episode, had a pretreatment score of 18 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item), clinical indication for ECT, and provided written informed consent. Patients were excluded with a history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar disorder, neurologic illness or insult, alcohol, or other drug abuse within the past year, ECT within the past 6 months, or severe medical illness.
Baseline patient characteristics:	Of the 90 patients in the sample, 57% were female. Average age (mean ± SD) was 51 ± 16, education averaged 15 ± 3 years, and total IQ averaged 105 ± 19. Patients averaged 14 ± 7 days of medication washout before starting ECT. The average baseline HRSD and BDI scores were 30 ± 7 and 34 ± 11, respectively, indicating severe symptomatology by both clinician rating and self-report. The average Global Assessment Scale (GAS) score was 41 ± 8, indicating marked functional disability. Patients received on average 6 ± 4 antidepressant medication trials in the current episode prior to ECT, of which 2.2 ± 2 were rated as failed adequate trials; 77% of the sample met Antidepressant Treatment History Form (ATHF) criteria for medication resistance. Bipolar depression characterized 30% of the sample and 17% of the patients had psychotic features. The average duration of the current episode was 29 ± 33 months (120 month cutoff), with 3 ± 3 previous episodes of mood disorder and 2 ± 3 prior psychiatric hospitalizations. This inpatient sample was comprised of severely depressed, highly disabled patients, with largely recurrent and treatment-resistant mood disorder. Approximately, 50% of this sample attempted suicide in the current episode, prior to receiving ECT. Demographic and clinical characteristics did not differ among the 4 randomized treatment groups (pulse width by electrode placement), except for a higher representation of psychotic depression in the two ultrabrief pulse treatment groups.
Primary effectiveness endpoints:	The a priori effectiveness endpoints were HRSD scores and remission rates one week following the ECT course, as well as relapse rates in patients who responded over the subsequent 52 weeks. Remission was defined as a HRSD (24-item) score ≤ 10 one week following the randomized ECT course.
Primary safety endpoints:	A set of a priori cognitive outcomes were specified separately for acute, short-term, and long-term time points. Primary cognitive outcomes included time to achieve re-orientation in the acute postictal period and scores on the Columbia University Autobiographical Memory Interview (CUAMI)

	following the randomized ECT course and at two month and six month follow-up. Other primary cognitive outcomes were measures of anterograde and retrograde memory during the acute and short-term (week following ECT) time frames.
Key secondary endpoints:	Secondary endpoints included potential differences among the four treatment groups (pulse width by electrode placement) in dosing requirements (initial seizure threshold) and in subjective ratings of cognitive change. Secondary efficacy measures included the Beck Depression Inventory (self-report) and clinician ratings (CGI-S, response status), and the treatment groups were also compared in the number of ECT treatments administered. A large neuropsychological battery was administered at each treatment session and prior to and following the ECT course, providing multiple secondary cognitive measures. Subjective effects of ECT on both mood and cognition were also evaluated.
Clinical results effectiveness:	Pulse width interacted with electrode placement on efficacy measures (see table below). Ultrabrief BL ECT had significantly weaker efficacy than the other three groups, which did not differ. Remission rates one-week following ECT was 35% (8/23) for ultrabrief BL ECT, and 73% (16/22) for ultrabrief RUL ECT, 65% (15/23) for brief pulse BL ECT and 59% (13/22) for brief pulse RUL ECT. HRSD scores showed greater improvement in all groups compared to ultrabrief BL ECT. Average HRSD scores (mean±SD) before and one week following ECT dropped from 32±8 to 19±12 for ultrabrief BL ECT (n=23), and from 30±7 to 11±9 for ultrabrief RUL ECT (n=22), from 31±7 to 12±8 for brief pulse RUL ECT (n=22), and from 29±7 to 12±10 for brief pulse BL ECT (n=23). Of 65 patients clinically monitored following response or remission with ECT, 26 patients (40%) completed the 1-year monitoring without relapse, 34 patients (52%) relapsed, and five patients (8%) left the study before the 1-year observation period was completed. The form of ECT used to achieve improvement was not related to likelihood or speed of relapse.
Clinical results safety:	The ultrabrief RUL group had less severe cognitive side effects than the other three groups in virtually all primary outcome measures assessed in the acute postictal period, and during and immediately after ECT (see Tables below). Both the ultrabrief stimulus and right unilateral electrode placement produced less short- and long-term retrograde amnesia. Patients treated with ultrabrief stimulation had less retrograde amnesia for autobiographical information (CUAMI) at assessments immediately following ECT and two and six months after ECT (see Tables below). For example, the time to full reorientation in the acute postictal period averaged 10±6 minutes for ultrabrief RUL ECT (n=22), 14±7 minutes for ultrabrief BL ECT (n=23), 22±9 minutes for brief pulse RUL ECT (n=22), and 33±21 minutes for brief pulse BL ECT (n=21). Other than orientation recovery, all cognitive measures were standardized relative to the distribution of scores at pre-ECT baseline. For the measure of retrograde memory for autobiographical information, scores were also adjusted for the extent of inconsistency in memory recall over a 4 week period in a sample of healthy controls. When assessed during the week following the randomized ECT course, the ultrabrief RUL ECT group (n=20) averaged 0.0±1.0 on this measure, indicating no difference in recall consistency relative to healthy controls over a comparable interval. In contrast, the scores were -0.4±1.1 for ultrabrief BL ECT (n=22), -1.0±1.0 for brief pulse RUL ECT (n=19), and -1.4±1.0 for brief pulse BL ECT (n=17). At this assessment, all groups differed significantly from each other. Six months following ECT, patients treated with only ultrabrief RUL ECT (n=10) averaged 0.1±1.0 on this measure, and the ultrabrief BL ECT group (n=10) averaged -0.1±0.8, the brief pulse RUL ECT group (n=11) averaged -0.7±1.1 and the brief pulse BL ECT group (n=12) averaged -0.7±0.9. Patients who did not respond to their randomized ECT course were offered a second course using brief pulse BL ECT. this crossover group (n=18) had the greatest deficit at 6 months averaging -0.9±1.1.
Key secondary endpoints results	Seizure threshold was approximately 3-4 times lower in patients treated with the ultrabrief stimulus (0.3 ms) compared to the brief pulse (1.5 ms) stimulus. Patients rated their memory deficits as less severe after ultrabrief RUL ECT compared with each of the other three conditions (see Tables below). Other secondary effectiveness and cognitive endpoints

(see Tables below) were consistent in indicating that ultrabrief RUL treatment had strong efficacy and diminished cognitive effects.

Primary and Secondary Efficacy Endpoints

	Ultrabrief RUL ECT (N = 22)	Ultrabrief BL ECT (N = 23)	Brief Pulse RUL ECT (N = 22)	Brief Pulse BL ECT (N = 23)
HRSD Scores				
Pre-ECT	30±7	32±8	31±7	29±7
Immediate post-ECT	10±9[a]	18±13[b]	10±8[a]	10±10[a]
One-week post-ECT*	11±9[a]	19±12[b]	12±8[a]	12±10[a]
Response Rates				
Immediate post-ECT (%)	77	48	73	70
One-week post-ECT (%)	73[a]	35[b]	59[a]	65[a]
Remission Rates				
Immediate post-ECT (%)	77[a]	43[b]	73[a]	70[a]
One-week post-ECT (%)*	73[a]	35[b]	59[a]	65[a]
CGI-I Response Rate (%)	82[a]	35[b]	64[a]	65[a]
Post-ECT GAS	64±12[a]	51±15[b]	63±11[a]	62±12[a]
Post-ECT BDI	10±11[a]	19±19[b]	11±8[a]	10±12[a]
Number of Treatments	8.7±2.4[a]	8.9±2.5[a]	8.5±2.5[a]	6.2±2.4[b]

Plus–minus values are means±SD. The treatment groups differed significantly in log-linear analyses or ANCOVAs, except in immediate response rate. Values with different letter superscripts for the same variable indicate that the corresponding treatment groups differed significantly from each other in post hoc pair-wise comparisons ($P<0.05$). Groups did not differ if they shared a superscript letter.
* Declared a priori as a primary efficacy outcome measure.

Primary and Secondary Outcomes: Acute Effects on Orientation Recovery and Cognitive Functions

	Ultrabrief RUL ECT (N = 22)	Ultrabrief BL ECT (N = 23)	Brief Pulse RUL ECT (N = 22)	Brief Pulse BL ECT (N = 23)
Post-ictal Orientation Recovery				
Time to recovery of orientation (min)*	10±6[a]	14±7[b]	22±9[c]	33±21[d]
Treatment sessions with prolonged disorientation (%)	0.0±0.0[a]	0.4±1.7[a]	1.1±3.5[a]	10.0±24.6[b]
Retrograde Memory				
Word recall	-0.5±0.8[a]	-0.7±0.5[a,b]	-1.0±0.4[b]	-1.1±0.4[b]
Word recall and recognition*	-0.4±0.9[a]	-0.7±0.8[a]	-1.3±1.1[b]	-1.4±0.9[b]
Geometric shape recognition*	-0.1±0.4[a]	-0.2±0.6[a]	-0.8±0.9[b]	-0.8±0.8[b]
Nonsense shape recognition*	0.0±0.6[a]	0.0±0.5[a]	-0.3±0.8[a,b]	-0.4±0.7[b]
Neutral face recognition	-0.9±0.9[a]	-1.3±1.0[a,b]	-1.5±1.1[b]	-1.7±0.9[b]
Anterograde Memory				
Affective face recognition*	-0.8±1.1	-0.8±0.8	-1.1±1.0	-1.2±0.8
Sentence recognition*	-0.6±0.8[a]	-1.1±0.6[b]	-2.0±0.8[c]	-1.7±0.9[c]
Sentence temporal order	-0.7±0.5	-0.7±0.5	-0.6±0.9	-0.8±0.7
Cancellation Performance				
Omission Errors	-0.8±0.9[a]	-0.9±1.0[a,b]	-1.4±1.0[b]	-1.1±1.1[a,b]
Commission Errors	-0.3±0.8[a]	-0.4±0.9[a]	-1.0±1.2[b]	-0.8±1.0[a,b]

Verbal Fluency

Letter	-0.7±0.7	-0.6±0.8	-0.6±0.7	-0.9±0.7
Category	-0.3±1.1[a]	-0.6±0.7[a,b]	-0.8±0.7[b]	-0.9±0.6[b]
Language				
Visual confrontation naming	0.2±0.8[a]	-0.2±1.0[a,b]	-0.6±1.3[b]	-0.4±1.2[a,b]
Naming from verbal description	-0.0±0.9	-0.1±0.6	-0.3±1.3	-0.5±0.9

Plus–minus values are means±SD. Acute cognitive testing was conducted at every treatment session and averaged over the complete treatment course. Higher values indicate greater impairment for the 2 orientation measures. For all other measures, scores are in standardized units relative to the sample performance prior to ECT and reflect change from pre-ECT baseline. For these measures, lower values indicate greater impairment. Cognitive measures with letter superscripts yielded significant treatment groups differences in ANCOVAs controlling for age, number of treatments, and baseline score. Values with different letter superscripts differed significantly from each other in post hoc t-tests on least-squares adjusted means (P<0.05).
* Declared a priori as a primary cognitive outcome measure.

Primary and Secondary Outcomes: Short-term Effects on Objective and Subjective Cognitive Functions

	Ultrabrief RUL ECT (N = 22)	Ultrabrief BL ECT (N = 23)	Brief Pulse RUL ECT (N = 22)	Brief Pulse BL ECT (N = 23)
Global Cognitive Status: Modified Mini-Mental State Exam				
Post-Six ECT	+0.0±1.1[a]	-0.1±0.9[a]	-1.3±1.9[b]	-1.0±1.7[b]
Post-Treatment Course*	+0.2±1.0[a]	-0.2±1.0[b]	-0.6±1.2[b]	-0.6±1.1[b]
Anterograde Memory: Delayed Reproduction Complex Figure Test				
Post-Seven ECT	-0.1±0.9[a]	-0.1±0.9[a]	-0.3±0.8[a,b]	-0.5±0.6[b]
Post-Treatment Course*	+0.2±1.0[a]	+0.1±0.8[a]	-0.3±0.9[b]	-0.4±0.7[b]
Anterograde Memory: Delayed Recall Buschke Selective Reminding Test				
Post-Six ECT	+0.4±1.1[a]	+0.3±0.9[a]	-0.4±1.0[b]	-0.3±0.7[b]
Post-Treatment Course*	+0.3±1.0[a]	+0.2±0.9[a,b]	-0.2±1.2[b]	-0.1±0.7[b]
Anterograde Memory: Randt Story Recall at 24 Hr Delay				
Post-Six ECT	-0.2±0.9	-0.3±1.2	-0.9±0.7	-0.7±1.1
Post-Treatment Course	+0.1±1.1[a]	-0.2±1.2[a,b]	-0.6±0.8[a,b]	-0.7±1.2[b]
Retrograde Autobiographical Memory: Columbia University Autobiographical Memory Interview				
Post-Treatment Course*	0.0±1.0[a]	-0.4±1.1[b]	-1.0±1.0[c]	-1.4±1.0[d]
Retrograde Memory: Public Events				
Goldberg Public Events*	0.0±1.2[a]	-0.2±0.9[a]	-0.2±1.2[a]	-0.6±1.0[b]
Subjective Cognitive Evaluation				
Global Memory Assessment	-0.3±1.0[a]	-1.1±0.9[b]	-1.4±1.0[b]	-1.4±1.0[b]

Plus–minus values are means±SD. All scores are in standardized units relative to the sample performance prior to ECT and reflect change from pre-ECT baseline. Cognitive measures with letter superscripts yielded significant treatment groups differences in ANCOVAs controlling for age, number of treatments, and baseline score. For all measures, lower values indicate greater impairment. Values with different letter superscripts differed significantly from each other in post hoc t-tests on least-squares adjusted means (P<0.05).
* Declared a priori as a primary outcome measure.

Adverse events and side effects	Adverse event rates and rates of systemic side effects were not reported.
Study conclusions	"The use of an ultrabrief stimulus markedly reduces adverse cognitive effects, and when coupled with markedly suprathreshold right unilateral ECT, also preserves efficacy."

Sackeim et al (2009): Optimization of ECT Multi-Site Trial

Authors:	Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, Isenberg K, Garcia K, Mulsant BH, Haskett RF.
Title:	Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects
Major Publication:	Arch Gen Psychiatry. 2009;66:729-737.
Study site(s):	Wake Forest University Health Sciences, Western Psychiatric Institute and Clinic/University of Pittsburgh, and Washington University, St Louis were study sites, and the New York State Psychiatric Institute/Columbia University was the coordinating/monitoring center.
Study protocol:	Prospective, multi-site, randomized, triple-masked, placebo-controlled study that tested the hypotheses that, compared with placebo, concomitant treatment with nortriptyline or venlafaxine during the ECT course enhances short-term efficacy without a meaningful effect on adverse effects, and the hypotheses that high-dose, right-sided, unilateral (RUL) ECT is equivalent in efficacy to moderate-dosage bifrontotemporal (BL) ECT and retains advantages with respect to cognitive adverse effects. Other than lorazepam, psychotropics were stopped prior to ECT. The intent-to-treat sample comprised 319 patients who were randomized to receive either low dose (1.5 x ST), brief pulse (1 ms), BL ECT or high dose (6 x ST), brief pulse (1 ms), RUL ECT. They were also randomized to treatment with nortriptyline, venlafaxine, or placebo starting the afternoon of the first ECT treatment, with the blind maintained by use of a "double dummy" technique.
Patient population studied:	Patients met DSM-IV criteria for a major depressive episode (unipolar or bipolar) using a formal structured interview and provided written informed consent. They scored 21 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item), and treatment with ECT was indicated. Patients were excluded if they had a history of schizophrenia, schizoaffective disorder, non–mood disorder psychosis, neurological illness, alcohol or drug abuse within 6 months, ECT within 6 months, or severe medical illness. Patients were also excluded if they had a known allergy or contraindication to nortriptyline or venlafaxine.
Baseline patient characteristics:	Of the 319 patients in the intent-to-treat sample, 64% were female. Average age (mean ± SD) was 49 ± 16, and had an average education of 14 ± 3 years. The average baseline HRSD and BDI scores were 31 ± 7 and 38 ± 10, indicating severe symptomatology by both clinician rating and self-report. The average Global Assessment Scale (GAS) score was 36 ± 10, indicating marked functional disability. Patients received on average 5 ± 4 antidepressant medication trials in the current episode prior to ECT, of which 1.3 ± 1 were rated as failed adequate trials. 79% of the sample met ATHF criteria for medication resistance. 21% of the sample had bipolar depression and 20% of the sample had psychotic features. The average duration of the current episode was 13 ± 18 months (120 month cutoff), with 3 ± 3 previous episodes of mood disorder and 2 ± 2 prior psychiatric hospitalizations. This mixed outpatient and inpatient sample was comprised of severely depressed, highly disabled patients, with largely recurrent and treatment-resistant mood disorder. There were no differences among the randomized pharmacological conditions and randomized ECT treatment groups in baseline demographic and clinical characteristics.
Primary effectiveness endpoints:	The a priori primary outcome measures were the HRSD scores 4 to 8 days following completion of all ECT and the rate of remission. Remission was defined as a HRSD (24-item) score ≤ 10 4 to 8 days following the randomized ECT course.
Primary safety endpoints:	Adverse effects were assessed in terms of the frequency of adverse and serious adverse events, scores on the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, and primary cognitive outcome measures from a neuropsychological battery.

<table>
<tr><td></td><td>The a priori primary cognitive outcomes were four measures from a considerably larger neuropsychological battery. These measures were obtained at baseline and within the week following ECT. The four measures were total score on the modified Mini-Mental State Examination (MMSE), accuracy (d') on the N-Back test, total recall of unrelated words across 6 trials of the Buschke Selective Reminding Test (BSRT), and score on the Columbia University Autobiographical Memory Interview, Short Form (CUAMI-SF).</td></tr>
<tr><td>Key secondary endpoints:</td><td>Assessment of integrity of the masks to treatment conditions by contrasting best guesses of patients and clinical raters of treatment conditions vs. actual assignments.

Secondary efficacy outcome measures were the CGI-S and Beck Depression Inventory-II scores following completion of ECT and the rate of response on the CGI-I, defined as a post-ECT score of 1 or 2. The treatment groups were also compared in the number of ECT sessions in the acute treatment course.</td></tr>
<tr><td>Clinical results effectiveness:</td><td>Treatment with nortriptyline enhanced the efficacy and reduced the cognitive adverse effects of ECT relative to placebo. Venlafaxine resulted in a weaker degree of improvement and tended to worsen cognitive adverse effects. High-dosage RUL ECT did not differ or was superior to BL ECT in efficacy and resulted in less severe amnesia (see Tables below). In the intent-to-treat sample, the remission rate was 51.8% (86/164) for low dose, brief pulse BL ECT and 61.3% (95/155) for high dose, brief pulse, RUL ECT. In the completer sample, the remission rates were 67.2% (86/128) and 76.0% (95/125) for the BL and RUL groups, respectively. See the Tables below for the primary and secondary efficacy endpoints.</td></tr>
<tr><td>Clinical results safety:</td><td>Results regarding adverse events and assessment of the systemic side effects are described below. While post-ECT deficits were observed with all 4 primary measures relative to pre-ECT baseline, the magnitude was substantially greater for the CUAMI-SF. There was a significant effect of pharmacological condition for 3 of the 4 measures, all reflecting a superiority of nortriptyline compared with either venlafaxine (MMSE, BSRT) or placebo (NBack). High dose RUL ECT resulted in less severe amnesia than BL ECT on the CUAMI-SF and BSRT. Older age was associated with greater post-ECT cognitive change.

Primary Cognitive Outcome Measures by the ECT Conditions
<table>
<tr><td></td><td colspan="4">ECT Condition</td></tr>
<tr><td>Post-ECT Cognitive Measure</td><td colspan="2">BL ECT</td><td colspan="2">RUL ECT</td></tr>
<tr><td></td><td>Mean±SD</td><td>N</td><td>Mean±SD</td><td>N</td></tr>
<tr><td>Columbia University Autobiographical Memory Interview (CUAMI-SF)</td><td>-3.1±1.6</td><td>110</td><td>-2.6±1.5</td><td>111</td></tr>
<tr><td>Mini-Mental State Exam (MMS)</td><td>-0.33±1.0</td><td>110</td><td>-0.25±1.0</td><td>123</td></tr>
<tr><td>Buschke Selective Reminding Test (BSRT)</td><td>-0.44±1.0</td><td>105</td><td>-0.28±1.0</td><td>113</td></tr>
<tr><td>N-Back (d')</td><td>0.05±1.0</td><td>76</td><td>-0.03±1.0</td><td>87</td></tr>
</table>
Plus–minus values are means±SD. All scores pertained to testing prior to crossover and are in standardized units relative to the sample performance prior to ECT. For all measures, lower values indicate greater impairment. ANCOVAs indicated that the RUL ECT group had superior post-ECT cognitive scores on the CUAMI-SF and BSRT amnesia measures.</td></tr>
<tr><td>Key secondary endpoints results</td><td>There was no association between the best guesses of either patients or clinical raters and actual treatment conditions indicating that the masks were effectively maintained.

The superiority of clinical outcome in the nortriptyline group with intermediate effects for venlafaxine were consistently observed across secondary efficacy measures, as were the differences favoring RUL ECT over BL ECT. There were no differences among the pharmacological or ECT treatment conditions in the number of ECT treatments administered.</td></tr>
</table>

<table>
<tr><td></td><td>
Primary and Secondary Efficacy Outcome Measures as a Function of Randomized Pharmacological and ECT Conditions
<table>
<tr><th></th><th colspan="3">Pharmacological Condition</th><th colspan="2">ECT Condition</th></tr>
<tr><th>Variable</th><th>Placebo</th><th>Nortriptyline</th><th>Venlafaxine</th><th>BL ECT</th><th>RUL ECT</th></tr>
<tr><td colspan="6">Intent-to-Treat Sample (N=319)</td></tr>
<tr><td>Post-ECT HRSD*</td><td>14.6±10.7</td><td>11.6±10.0</td><td>12.2±10.2</td><td>13.5±10.4</td><td>12.5±10.4</td></tr>
<tr><td>Remission, %*</td><td>48.9</td><td>63.4</td><td>60.4</td><td>51.8</td><td>61.3</td></tr>
<tr><td>Post-ECT CGI-S,</td><td>3.1±1.5</td><td>2.6±1.4</td><td>2.8±1.4</td><td>2.9±1.5</td><td>2.8±1.4</td></tr>
<tr><td>CGI-I Response, %</td><td>51.1</td><td>64.5</td><td>61.5</td><td>52.4</td><td>63.9</td></tr>
<tr><td>Post-ECT BDI</td><td>18.4±12.9</td><td>16.8±11.6</td><td>14.9±12.0</td><td>17.9±12.7</td><td>15.9±11.8</td></tr>
<tr><td>No. ECT Treatments</td><td>8.4±4.3</td><td>7.9±3.9</td><td>7.9±4.98</td><td>8.1±4.3</td><td>8.1±4.5</td></tr>
<tr><td colspan="6">Completer Sample (N=252)</td></tr>
<tr><td>Post-ECT HRSD</td><td>11.7±9.3</td><td>8.8±8.1</td><td>9.8±9.4</td><td>11.0±9.6</td><td>9.6±8.5</td></tr>
<tr><td>Remission Rate, %</td><td>62.3</td><td>79.7</td><td>76.7</td><td>67.2</td><td>76.0</td></tr>
<tr><td colspan="6">Intent-to-Treat Sample Prior to Crossover (N=319)</td></tr>
<tr><td>Post-ECT HRSD</td><td>15.9±10.7</td><td>12.6±9.8</td><td>13.0±9.7</td><td>14.4±10.1</td><td>13.8±10.4</td></tr>
<tr><td>Remission Rate %</td><td>41.4</td><td>54.8</td><td>52.8</td><td>45.7</td><td>48.6</td></tr>
</table>
Values are mean±SD. The ITT Sample comprised all patients all patients randomized to pharmacological and ECT treatment conditions, with endpoints 4-8 following completion of all ECT. Completer sample comprised patients who either were classified as remitters or who received at least 8 ECT treatments. The ITT Sample prior to Crossover used as endpoints HRSD scores restricted to those obtained following the randomized ECT treatment course.
* Declared a priori as a primary efficacy outcome measure. ANCOVA on the primary post-ECT HRSD score (ITT Sample) yielded a significant effect of pharmacological condition, while logistic regression on the remission rate yielded significant main effects of pharmacological condition and ECT condition. Post-ECT HRSD scores were higher and the remission rate lower in the placebo than nortriptyline group, while the remission rate was higher in patients randomized to RUL ECT.
</td></tr>
<tr><td>Adverse events and side effects</td><td>A single adverse event was experienced by 22 patients, 5 had 2 adverse events, 9 had a serious adverse event, and 2 experienced both an adverse event and a serious adverse event. The most common adverse event was a cardiac complication (n=13), typically manifesting as sustained tachycardia and/or hypertension after seizure determination, and managed with a beta-blocker medication. The most common serious adverse events were suicide attempt (n=3), delirium (n=2), and an intercurrent illness requiring hospitalization (n=2). Analyses of covariance did not reveal any difference among the randomized treatment conditions in number of adverse events and/or serious adverse events.

Systemic side effects were assessed with the UKU before starting ECT and then regularly during the ECT course. These scores improved markedly during the ECT course, and the degree of improvement was associated with the change in HRSD scores. There were no differences among the randomized ECT and pharmacological conditions in the change in reports of systemic side effects on the UKU.</td></tr>
<tr><td>Study conclusions</td><td>“The efficacy of ECT is substantially increased by the addition of an antidepressant medication, but such medications may differ in whether they reduce or increase cognitive adverse effects. High-dose, right-sided, unilateral ECT is at least equivalent to moderate-dosage bilateral ECT in efficacy, but retains advantages with respect to cognitive adverse effects.”</td></tr>
</table>

Semkovska et al (2016): Enhancing the Effectiveness of Electroconvulsive Therapy in Severe Depression - (EFFECT-Dep) Study

Authors:	Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, Noone M, Carton M, Lambe S, McHugh C, McLoughlin DM.
Title:	Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): A Pragmatic, Randomized, Non-Inferiority Trial
Major Publication:	Arch Gen Psychiatry. 2009;66:729-737.
Study site(s):	St. Patrick's Mental Health Services/Trinity College Dublin, Ireland
Study protocol:	Prospective, pragmatic, patient- and rater-blinded, two-group parallel, randomized, noninferiority trial with a 6-month follow-up. One hundred forty patients (138 in intent-to-treat sample) were randomized to high dose (6 x ST), brief pulse (1 ms), right unilateral (RUL) ECT or moderate dose (1.5 x ST) bifrontotemporal (bilateral, BL) ECT with equal allocation, with the randomization stratified by age (≥ 65 years: yes/no), previous ECT (yes/no), and referral site. Patients and assessors were all masked to treatment condition and integrity of masking was tested after end-of-treatment assessments by asking patients and raters to guess the treatment used. In this pragmatic trial, psychotropic medications were not constrained. The number of ECT sessions was determined by referring clinicians in consultation with patients, up to 12 sessions in accordance with recommendations of the Irish Mental Health Commission. This randomized trial has tested the hypotheses that twice weekly high-dose (6 x ST) RUL ECT is noninferior to reference (1.5 x ST) BL ECT in efficacy and superior in terms of cognition and retrograde memory preservation over a prolonged follow-up period. The short- and long-term effectiveness and cognitive side effects of high-dose RUL and moderate-dose BL ECT were compared over a 6 month follow-up period in patients with severe depression receiving ECT in routine practice.
Patient population studied:	Participants met DSM-IV criteria for a major depressive episode (unipolar or bipolar) using a formal structured interview. They were ≥ 18 years old, referred for ECT, scored ≥ 21 on the 24-item Hamilton Rating Scale for Depression (HRSD), and provided written informed consent. Exclusion criteria were conditions rendering patients unfit for general anesthesia or ECT; ECT in previous 6 months; history of schizophrenia, schizoaffective disorder, or neurodegenerative or other neurological disorder; alcohol/substance abuse in the previous 6 months; involuntary status; and inability/refusal to consent.
Baseline patient characteristics:	Of the 138 patients in the intent-to-treat sample, 63% were female. Average age (mean ± SD) was 57 ± 15, and education averaged 13 ± 3 years. The average baseline HRSD score was 30 ± 6, indicating severe symptomatology. The average Clinical Global Impression-Severity score rated by the referring physician of 5.3 ± 0.7 also indicated a judgment of severe disturbance. Before and during treatment with ECT patients received on average 4 ± 1 psychotropic medications. 73% of the sample met ATHF criteria for medication resistance. 23% of the sample had bipolar depression and 21% of the sample had psychotic features. The median duration of the current episode was 20 weeks (104 week cutoff), with a median of 4 previous episodes of mood disorder. This sample was comprised of severely depressed patients, with largely recurrent and treatment-resistant mood disorder. The primary overlapping reasons for referral to ECT by the referring physician were refractory to medication (75%), rapid response required (57%), acute suicidality (5%), and physical deterioration (1%). There were no differences between the randomized ECT treatment groups in baseline demographic and clinical characteristics.
Primary effectiveness endpoints:	The a priori primary outcome was depression severity measured by the 24-item HAM-D after completing the ECT course (end of treatment).

Primary safety endpoints:	Common adverse physical effects (nausea, headache, muscle aches) were recorded for each session to measure occurrence (yes/no) within each course. Serious adverse events that required prolonged medical attention or were life-threatening were recorded. The a priori primary cognitive outcome was scores on the Columbia University Autobiographical Memory Interview, Short Form (CUAMI-SF), a measure of retrograde amnesia for autobiographical information.
Key secondary endpoints:	Assessment of integrity of the masks to treatment conditions by contrasting best guesses of patients and clinical raters of treatment conditions vs. actual assignments. Secondary depression outcomes included HRSD scores at the 3- and 6-month follow-ups, end-of-treatment remission and response status, and relapse status for remitters during the 6-month follow-up. The treatment groups were also compared in the number of ECT sessions in the acute treatment course. Secondary cognitive outcomes included standardized measures of global cognition (Mini-Mental State Examination [MMSE]), auditory attention and verbal working memory (digit spans forward and backward), psychomotor speed and executive function (Trail-Making Test, parts A and B), semantic memory (category fluency), verbal learning and delayed recall (Free and Cued Selective Reminding Test), and visuo-spatial functioning and memory (Complex Figures Test). Cognitive outcomes were assessed at baseline, end of treatment, and 3- and 6-month follow-ups. Time to recover orientation was also assessed at each ECT session. Subjective symptoms attributable to ECT were assessed with the Columbia ECT Subjective Side Effects Schedule, including six items on memory, concentration, and orientation for self-rating of cognition.
Clinical results effectiveness:	High-dose unilateral ECT was noninferior to bitemporal ECT at the end of treatment and at the subsequent time points. The nonsignificant differences between the treatment groups favored RUL ECT. At end of treatment, HRSD scores decreased from an average of approximately 30 in both groups to 12 in the BL ECT group (N=69) and 11 in the RUL ECT group (N=69).
Clinical results safety:	Autobiographical memory scores for the RUL (46.9±9.7, N=66) and BL ECT (44.4±10.3, N=64) groups were similar at baseline. The percent consistency of recall of baseline memories (primary measure) was significantly lower in the BL group at the end of treatment (odds ratio=0.66, 95% CI=0.513–0.85, p=0.001; RUL ECT, N=64; BL ECT, N=64), and this difference remained significant at the 3-month (odds ratio=0.59, 95% CI=0.45–0.78, p<0.001; RUL ECT, N=56; BL ECT, N=48) and 6-month (odds ratio=0.59, 95% CI=0.45–0.79, p<0.001; RUL ECT, N=49; BL ECT, N=42) follow-up assessments.
Key secondary endpoints results	*Efficacy:* The ECT treatment groups did not differ in response rates [RUL: 61% (42/69), BL: 51% (35/69)] or remission rates [RUL: 46% (32/69), BL: 42% (29/69)]. Remission was defined as a HRSD (24-item) score ≤ 10 for 2 consecutive weeks following the randomized ECT course. There was no significant difference between the proportion of remitters who relapsed in the unilateral (8/32; 25.0%) and bitemporal (11/29; 37.9%) groups over the 6-month follow-up. The treatment groups did not differ in number of treatments. *Cognition:* The RUL ECT group (median = 19.1 minutes) had significantly faster recovery of orientation in the postictal period than the BL ECT group (median = 26.4). There were scattered statistically significant differences between the treatment groups in other secondary cognitive measures, all of which favored the RUL ECT group. However, only the deficit on the CUAMI-SF consistently distinguished the groups at all post-ECT time points. *Masking Integrity:* There was no association between the best guesses of either patients or clinical raters and actual treatment conditions indicating that the mask was effectively maintained.

	Subjective Cognitive Assessment: Significantly fewer subjective cognitive side effects were reported by the RUL ECT group at the end of treatment and after 6 month follow-up.
Adverse events and side effects	Regarding major adverse events, six patients required beta-blockers for ECT-related hypertension (RUL, N=4; BL, N=2). In the RUL ECT group, one patient developed laryngospasm with temporary drop in oxygen saturation, one developed tachyarrhythmia necessitating ECT termination, and one attempted suicide during the course. In the BL ECT group, three patients developed interictal confusion resulting in postponement/termination of ECT, one developed bronchospasm, one required beta-blocker treatment for sinus tachycardia, one developed bradyarrhythmia, and one developed a pulmonary embolus after the fifth treatment. None of these events led to trial dropout. There were no differences between the RUL and BL groups for occurrence of headaches (26.5% versus 27.5%), nausea (16.2% versus 11.6%), or muscle pain (11.8% versus 8.7%).
Study conclusions	"Twice-weekly high-dose unilateral ECT is not inferior to bitemporal ECT for depression and may be preferable because of its better cognitive side-effect profile."

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