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## Evidence-Based Electroconvulsive Therapy for Major Depression Disorder

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### ABSTRACT

Electroconvulsive Therapy (ECT) is a treatment that steals medical attention and the public. Memory disturbance after ECT is a special consideration for the Food and Drugs Administration (FDA) of the United States to classify ECT, whether it belongs to class III (high risk). Psychiatrists or anesthesiologists (who are experienced with ECT) tend to change this classification, while neurologists, psychologists, biostatistics experts, and public representatives agree to maintain ECT status in class III. Contrary to unexpected effects, ECT can induce a transition in severe melancholic patients and suicide to normal functioning humans, after other treatments have failed. With the aim of balancing effectiveness and safety, this paper provides modern evidence of the benefits and risks of ECT.

### 1. Introduction

Electroconvulsive Therapy (ECT) is a treatment that receives medical attention and the public. In popular films and politically oriented journalism, ECT is described as an inhumane act. This picture is supported by antipsychiatric groups and causes restrictions on the use of ECT in many countries. In Scandinavian countries and several other countries, this therapy is a treatment needed for severe depression and other severe mental disorders. The cause of the controversy over the use of ECT is the cognitive side effects caused by this action. Memory impairment after ECT is a special consideration for the Food and Drugs Administration (FDA) of the United

States to classify ECT, whether it belongs to class III (high risk) medical equipment, which requires premarket approval, or is classified as class II (moderate risk, without requiring these requirements).<sup>1-6</sup> Psychiatrists or anesthesiologists (who are experienced with ECT) tend to change this classification, while neurologists, psychologists, biostatistics experts, and public representatives agree to maintain ECT status in class III. Memory impairment and the risk of inducing cerebral lesions are focused on by the anti-ECT group of the Committee for Truth in Psychiatry and successors, who have experienced extensive memory loss after ECT.

Contrary to unexpected effects, ECT can induce a transition in severe melancholic patients and suicide to normal functioning humans, after other treatments have failed. With the aim of balancing effectiveness and safety, this paper provides modern evidence of the benefits and risks of ECT.<sup>7,8</sup>

### **Indication**

For more than 70 years, indications of ECT focused on psychotic depression, severe depression with a risk of suicide, and other mental disorders with a high risk of lethal outcome (delirious mania, catatonic stupor, postpartum psychosis, cycloid psychosis, lethal catatonia, and malignant neuroleptic syndrome). On major indications of psychotic depression (with delusions and/or hallucinations), the rate of remission is 92-95 percent, compared with 55-84 percent in non-psychotic melancholic depression. The daily administration of imipramine 200-350 mg causes remission in 40 percent of patients with psychotic depression, while 83 percent of patients who do not respond to treatment improve after ECT. The combination of antipsychotics in therapies using anti-depressive drugs does not significantly increase its effect. In addition, this combination triggers the risk of weight gain and extrapyramidal side effects, especially in the elderly. The American Psychiatric Association recommends ECT as a treatment option for psychotic depression. In cases of non-psychotic melancholic depression, ECT is superior to drugs and is usually considered when the effects of the drug are inadequate. A meta-analysis shows ECT has more efficacy than ECT-stimulated and antidepressant drugs. The risk of suicidal tendencies in depression decreases faster with ECT compared to drugs and places ECT as the treatment of choice in depression with suicidal tendencies.<sup>9-14</sup>

### **Continuous ECT**

After ECT is successful, the risk of relapse is more than 80 percent in a year, making maintenance therapy necessary. ECT is ongoing at successive intervals after an acute episode and is an alternative

choice to prevent recurrence and disease recurrence. Studies in the United States showed a combination of nortriptyline and lithium is likely to cause recurrence for 6 months by 39 and 32 percent, whereas on placebo administration it is likely to relapse by 84 percent and 37 percent with 10 ECT treatments with increasing intervals. Subjective memory and appearance in several memory tests increased during stabilization treatment and there were no cognitive differences between treatments. Previous studies on continued treatment with meprobamate and paroxetine reduced the rate of relapse to 20-30 percent for 6 months, but the results of this study have never been replicated.<sup>15-17</sup>

If ECT is ongoing and medications are combined, the risk of relapse may be greater. In an open study, the chance of recurrence was seven percent over 2 years compared to 52 percent with only drugs. After 5 years, the recurrence rate will be 27 and 82 percent, respectively. The recurrence time was also getting longer. A naturalistic study of 4 patients who received drugs (antidepressants, antiepileptics, neuroleptics, and or lithium) along with ECT continued for 3 years showing a 75 percent reduction in hospitalization requirements compared to the previous 3 years.<sup>14-16</sup>

### **Memory disturbance**

Temporary memory disorders are an inevitable side effect of ECT that does not contribute to the antidepressant effect. The inability to remember not only consists of the period of therapy but also in memories before and after therapy. Memory impairment before therapy – retrograde amnesia – includes personal data and public events. There is a time gradient in the memory of events that occur close to ECT is also affected, especially in the period of 6 months before therapy. Impaired memory of events after therapy – anterograde amnesia – is the inability to receive new information/knowledge. The more therapy is given and the shorter the time period, the more tangible and longer the memory disturbance.<sup>17,18</sup>

Objective memory loss is usually shorter in terms than subjective memory loss, most studies indicate the

return of memory function to a pre-ECT degree or improvement in memory function within 2-6 months.

However, naturalistic studies using bitemporal sine wave stimulation show impaired personal memory recall 6 months after ECT. A meta-analysis of 2981 patients showed that cognitive side effects of ECT mainly occurred in the first 3 days after treatment and all cognitive functions improved compared to the conditions before therapy. Computer tomography and magnetic resonance imaging before and after ECT therapy did not show any lesions in the brain. Persistent memory loopholes after a series of ECT treatments are not only caused by ECT but are also based on mental disorders. This is also related to the condition of human life, that is, personal memory will gradually disappear if it is not regularly repeated. There is no test for retrograde amnesia in standardized ECT studies for normal forgetfulness. It can be concluded that ECT should be carried out according to the indications and expected benefits.<sup>19,20</sup>

#### Pathophysiology of Depression

Major depression may have toxic effects on the brain, which is manifested as hippocampal volume shrinkage. The longer the duration of the depressive episode, the more visible the hippocampal volume decreases. Because the severity of depression is related to cortisol levels in the blood, which then become normal when depression is cured, the decrease in the hippocampus may be caused by an increase in cortisol levels in the blood long-term or periodically. When hormone balance improves after ECT, the volume of the hippocampus increases.<sup>18,19</sup> In rats, electrically induced seizures stimulate the formation of new neurons, glial cells, and blood vessels. In this animal model of ECT, the formation of new neurons is greater than that of antidepressant drugs. Because there is a new formation of the whole structure, it is not possible that the increase in glia is a consequence of the loss of neurons. Microglia control the formation and development of new neurons. A hypothesis has been introduced that depression originates from glial cells.<sup>17-19</sup>

It has been estimated that ECT works by regulating hypothalamic control of the neuroendocrine system, which is demonstrated through normalization of cortisol levels in the blood. The importance of increased hippocampal cannot be determined. New cells are formed without the need for an antidepressant effect and the drug may have an antidepressant effect, but not accompanied by new cell formation.<sup>21</sup>

#### ECT application

Through ECT, severe depression usually decreases after the first therapy. As a rule, twelve partial therapies are needed every two or three days. In previous studies of endogenous depression (correspondents to melancholic depression), no more than 6 to seven treatments on average are needed for clinical remission. A multicentral study by the America CORE group in the same type of patient showed that 64 percent of patients experienced remission after an average of 7.3 treatments.<sup>21</sup>

In recent years, there is a tendency for acute series extension and a reduction in the rate of remission compared to before. This is the principle of more careful research about praxis treatment. Associated with decreased memory impairment, modified sine waves or sine waves have been substituted with short waves or ultra-brief waves and the position of bitemporal electrodes has been replaced by right unilateral stimulation.<sup>21</sup>

#### Seizure induction

In Scandinavia and many other European countries, Siemens Convulsator has become the choice of equipment for routine use and research. This tool can distribute unilateral pulses 5 ms at a frequency of 50 Hz continuously or in groups in 4 pulsations, with a reduction in frequency up to 25 Hz. The maximum filling is generally higher than modern equipment but the low-frequency rhythm and long stimulation time allow this equipment to adopt electrically individual doses by stopping stimulation at the beginning of the tonic phase in seizures. Modern

equipment transmits bipolar pulses with strong currents up to 0.9 A for 8 seconds. The maximum frequency is 120 Hz, with pulses up to 240 pulses per second. High-frequency pulsation produces tonic contractions from muscles. This makes it impossible to see the onset of the tonic phase of the seizure and then the cessation of stimulation. Motor spasms should go through the tonic-clonic phase by respectively decreasing the frequency and stopping starting from the distal part of the body. The EEG pattern should show an increase in initial amplitude (neuron recruitment), a high frequency and amplitude spike period, a transition to spike and wave patterns, and a clear end followed by ictal depression. Pulsation rates should increase significantly during seizures, as blood pressure immediately after the seizure ends. Seizures are usually followed by postictal confusion when the patient is conscious.<sup>22</sup>

The total electric dose (charge) in milli-coulomb (strong current x time) is determined by the current strength, pulsation frequency, pulsation width, and total stimulus time. The relative importance of this parameter cannot be understood yet, but in the interval, the frequency of 30-60 Hz turns out to be less influential. Stimulation for 2 seconds is more efficient than for 1 second with the same electric dose.<sup>23</sup>

### Electrode Placement

When the electrode placement is changed from a bitemporal stimulus to a unilateral stimulus in the non-dominant hemisphere (usually the right), the position of D'Elia is recommended. Studies in Scandinavia with Siemens Convulsators show unilateral stimulation causes less memory impairment but produces the same antidepressant effect as bilateral stimulation.

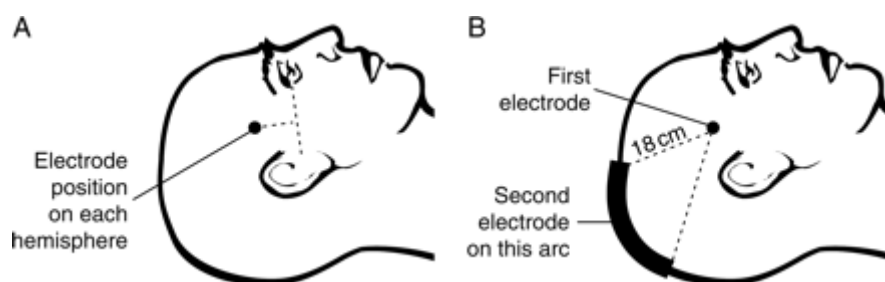


Figure 1. A. Bilateral ECT; B. Unilateral ECT with D'Elia Position (source: British Journal of Anesthesia)

In general, unilateral stimulation is more difficult to produce maximum seizures than bilateral stimulation. Besides stimulation above the threshold, anticonvulsant drugs and too-deep narcosis can prevent seizures during unilateral stimulation. Submaximal seizures occur more frequently in unilateral stimulation than bilateral stimulation and are a possible cause of the ineffectiveness of unilateral ECT.<sup>24</sup>

### Electric Dosage

High doses of ECT are more effective than low doses but tend to cause memory impairment. American investigators often trace seizure thresholds on first treatment - for example, the lowest amount of

electricity that induces epileptic activity. Titration shows the therapeutic effect of ECT varies according to the electrical dose-related to the seizure threshold. The condition for the satisfying effect of unilateral ECT is the electrical dose is a multiple of the seizure threshold. When unilateral stimulation is only 15 times the seizure threshold of 10.5 treatment is needed on average to achieve 55 percent remission in patients, although, referring to efficiency, bitemporal stimulation is applied after 5-8 initial therapies. When unilateral stimulation was increased to six times the seizure threshold and compared with bitemporal stimulation 1.5 times the seizure threshold, there were still fewer remissions (55 cons 64 percent) despite more therapy (5.9 cons 5.5). In addition, the effect of

unilateral stimulation is slower than bitemporal stimulation.

There is no difference in influence on memory functions and executive functions. Furthermore, unilateral stimulation has no cognitive advantage when it reaches a level that guarantees induction of seizures almost as well as anti-depressive effects after bitemporal stimulation.<sup>22,23</sup>

### **Pulsation width**

A good antidepressive effect with a high remission rate has been obtained through 5 ms pulsation in Scandinavia and 1 ms stimulation in American studies. A 0.5 ms pulse is recommended because it induces seizures with a heart rate of more than 1 ms pulsation, allowing indications of stronger and more general conduction activity. However, comparative studies are relatively small and do not provide conclusions about antidepressive effects. The reduction of ultra-brief stimuli (0.1-0.3 ms) results in submaximal seizures with antidepressive effects on bitemporal stimulation. When 1.0 ms pulsation is substituted with 0.3 ms pulsation on unilateral stimulation, the treatment series extends from nine to 12 treatment series.<sup>25</sup>

Ultra-brief pulsation (0.3-0.37 ms) on unilateral stimulation six times the seizure threshold requires more treatment than the same pulsation width as bitemporal stimulation 2.5 times the seizure threshold, which indicates the combination of ultra-brief pulsation and unilateral stimulation is less aligned. It is justified that ultra-brief pulsation allows the induction of seizures with low electrical doses, but although the same duration and pattern are the same as maximal seizures, the EEG shows atypical development and termination, increased heart rate and moderate blood pressure and the patient regains consciousness immediately after the seizure and is not confused. with the same degree of seizure after a grand mal seizure. Furthermore, the benefits of less memory impairment with ultra-brief pulsation are offset by lower antidepressive effects. However, the opposite result has been reported from the comparison between brief pulses (1.5 ms) and ultra-brief pulses (0.3 ms)

which are applied unilaterally or bitemporally. However, as retrograde amnesia is estimated to occur less with ultra-brief pulsation and unilateral stimulation, Eil unilateral ultra-brief results in remissions of 73 percent, unilateral ECT briefs 59 percent.<sup>25</sup>

### **2. Conclusion**

ECT can induce a transition in severe melancholic patients and suicide to normal functioning humans after other therapies have failed. With the aim of balancing effectiveness and safety, this paper provides modern evidence of the benefits and risks of ECT.

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