Optimal electrical stimulus during electroconvulsive therapy for depression: a national register-based randomized trial.

Synopsis

Aim: The purpose of the study is to determine the stimulus of electrical current during clectroconvulsive therapy (ECT) that produces the optimal balance between antidepressant effect and memory disturbance. Specifically, this study aims to compare the 0.5 ms and 1.0 ms pulse width stimuli.
Design: National, register-based randomized trial, unmasked with two treatment arms.
Primary objective: To test the hypothesis that a 1.0 ms pulse width stimulus produces a higher remission rate (< 11 on the MADRS-S) than a 0.5ms pulse width stimulus.
Secondary objectives include testing for differences in:

- self-rated global health measured with the EQ5D-VAS
- subjective memory worsening (increase of 2 on the memory item of the CPRS)
- antidepressive response (decrease of 50% on the MADRS-S)
- number of ECTs in the treatment series
- readmission and suicide rate within 6 months

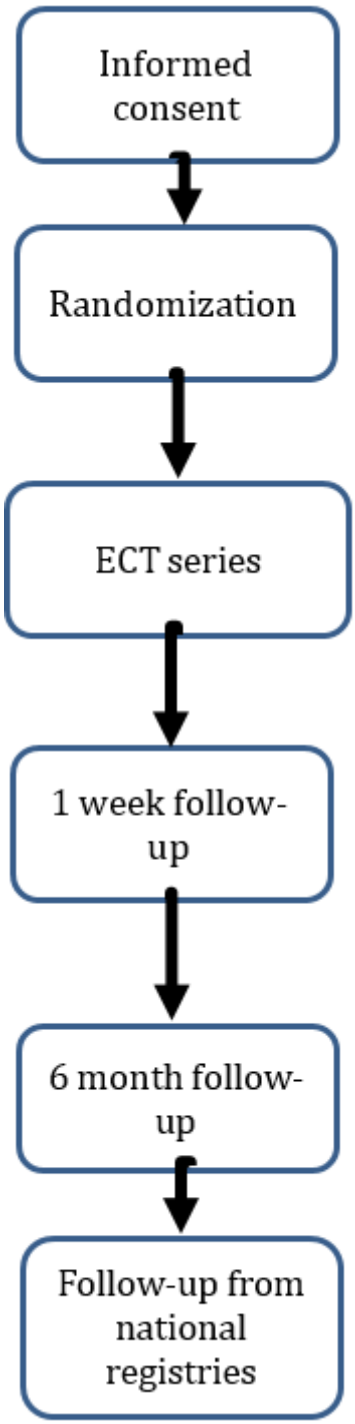
Study population: patients with unipolar or bipolar depression.
Sample size: 800 patients, 400 patients in each arm.
Inclusion criteria:

- At least 18 years of age at the time of inclusion
- Diagnostic criteria fulfilled for unipolar, or bipolar depressive episode according to ICD-10.
- An indication for and accepting ECT
- A Swedish personal identity number.
- Capable of giving informed consent.

Exclusion criteria:

- If the investigator judges a certain pulse width to be inappropriate for the patient.

Inclusion time 2019-05-01–2022-11-15.



Abbreviations

1. CGI: Clinical Global Impression Scale
2. CPRS: The Comprehensive Psychopathological Rating Scale
3. ECT: Electroconvulsive therapy
4. EQ5D: EuroQual-group 5 Dimensions Scale
5. ICD-10: International Statistical Classification of Diseases and Related Health Problems. - 10th revision,
6. MADRS-S: Montgomery-Åsberg Depression Rating Scale, self assessed version.
7. Q-ECT: Swedish national quality register for ECT
8. VAS: Visual analogue scale

Purpose and aims

The purpose of the study is to determine the electrical current stimulus for electroconvulsive therapy (ECT) that produces the optimal balance between antidepressant effect and memory disturbance. Specifically, this study aims to compare 0.5 ms and 1.0 ms pulse width stimuli.

Primary objective: To test the hypothesis that a 1.0 ms pulse width produces a higher remission rate (< 11 on the Montgomery-Åsberg Depression Rating Scale, self assessed version (MADRS-S)) than a 0.5 ms pulse width within 1 week after the treatment series.

The secondary objectives are to test for differences in:

1) self-rated global health measured with the EuroQual-group 5 Dimensions Scale Visual analogue scale (EQ5D-VAS)
2) subjective memory worsening (increase of 2 on the memory item of the Comprehensive Psychopathological Rating Scale (CPRS))
3) antidepressive response (decrease of 50% on the MADRS-S)
4) number of ECTs in the treatment series
5) readmission and suicide rate within 6 months
6) self-rated global health measured with the EQ5D-VAS at 6 month follow-up
7) subjective memory worsening (increase of 2 on the memory item of the CPRS) at 6 month follow-up
8) remission rate (< 11 on MADRS-S) at 6 month follow-up

Hypotheses:

1: The longer pulse width produces a higher remission rate (MADRS-S < 11) than the shorter pulse width within 1 week after treatment.
2: The longer pulse width produces a higher self-rated health status (EQ5D VAS) than the shorter pulse width within 1 week after the treatment.
3: The longer pulse width produces higher rates of subjective memory worsening than the shorter pulse width.
4: The longer pulse width produces a more rapid antidepressive effect than the shorter pulse width (fewer ECTs per treatment series).
5: The longer pulse width produces fewer relapses (rehospitalizations and suicides) than the shorter pulse width within 6 months after the treatment.
6: There are differences in the optimal pulse width between subgroups of patients based on sex, age-group, or initial psychosis status.

State of the art

Depression entails suffering and work impairment, and is a burden to kindred (1). Depression is a common disease. The one-month prevalence of major depression is estimated to be between 1.5 and 3% (2), and the one-year prevalence is estimated to be 8.6% (3). This high prevalence makes depression one of the most common causes of handicap worldwide (4); thus significant costs are associated with depression (5). The prognosis for depression is often unfavorable, and repeated relapses or chronicity occur in 70–80% of patients, and approximately 10% of affected individuals commit suicide (6).

Pharmacotherapies and cognitive behavioral therapies, are effective treatments for depression (7, 8). About one-third of patients who are exposed to one of these treatments become free of their symptoms, while another one-third of the patients improve but have some residual symptoms. The other one-third does not improve, despite these treatments (9, 10).

ECT is markedly more effective for treating depression than pharmacotherapies (11). In clinical trials, 60–70% of ECT patients with severe depression become free of symptoms (11, 12).
ECT is administered during a short anesthesia, with a treatment series usually consisting of 6–12 treatments over a 2–4 week period. A significant improvement in mental state is often observed after

a few treatments, but in some cases, as many as 20 treatments may be necessary (13). Indications for ECT include the need for a rapid and definitive response, or a lack of response to antidepressant medications (13, 14). It is estimated that one million patients worldwide receive ECT each year (15) and in Sweden, 4000 patients receive ECT annually (16).

The inducement of convulsion is an essential part of the treatment (17). Animal experiments show that seizures can stimulate cell replication in the hippocampus (18), and magnetic resonance imaging studies indicate increases in hippocampal volume following ECT in patients (19).

ECT has cognitive side effects, particularly on memory (20, 21). During a series of ECT sessions, memory encoding may be temporally impaired, although the ability to store memories tends to normalize within a few weeks (22) after treatment. However, some patients report memory disturbances long after termination of ECT. Whether these are effects of the treatment or of the disease is debated, since depressive disorders can negatively affect cognitive functioning (23), especially during the symptomatic state (24). Moreover, cognitive disturbances often persist for many years after episodes of severe depression, even in patients never treated with ECT (25).

There are two frequently used electrode placements: unilateral and bilateral placements (26). The unilateral d'Elia placement (27) is most commonly used in Sweden, as it is associated with a lower risk of amnesia and confusion (28). However, with bilateral electrode placement symptom reduction is faster and less electrical charges are necessary (28, 29).

Since the 1960s, the stimulus intensity and seizure length have been reduced. The modal pulse width has been reduced from 5 ms to 0.5 ms, and the mean seizure duration has decreased from 80 s to 30 s. These changes have been driven by studies showing that reduced stimulus intensities have a similar antidepressive effect, but result in lower memory disturbances. However, these studies have been underpowered in respect to the detection of clinically meaningful differences in antidepressive effects (28).

A recent meta-analysis showed that the 0.3 ms pulse width is inferior at producing antidepressant improvement as compared to the 1 ms pulse width, although this study also confirmed fewer temporary memory disturbances with the 0.3 ms pulse width (30). Following this meta-analysis, the 0.3 ms pulse width has been used less often. Instead, a 0.5 ms pulse width has been widely adopted, with hopes that it can retain the low level of memory disturbance associated with the 0.3 ms pulse width, but have the same antidepressant effect as the 1 ms pulse width (16). However, these assumptions are not proven; the 0.5 ms pulse width has not been systematically studied in clinical trials.

Significance and scientific novelty

A significant proportion of patients do not improve sufficiently with ECT, which poses a severe clinical problem. By the time ECT is considered, drug therapies are likely to have been tried, and the prognosis for these non-responders is already poor. Optimization of the effectiveness of ECT is therefore important.

We hypothesize that the quest for better tolerance during ECT has compromised its clinical efficiency, and that clinically relevant higher remission rates can be achieved with higher dosages than currently used. Many patients are required to test this hypothesis. The use of the Swedish intervention-based national quality registers to include large numbers of patients in randomized studies has been efficacious in other areas of medicine (31), although it has not yet been adopted in psychiatry.

Large randomized register-based trials allow clinical effects to be evaluated for subgroups. Women tend to require lower charges for the induction of seizures (32), and tend to be more vulnerable to memory disturbances (33). Nevertheless, no trial has investigated whether the pulse width producing

the optimal balance between memory disturbance and antidepressive effect differs between women and men, but we plan such an analysis.

Preliminary and previous results

Data from the Swedish national quality register for ECT (Q-ECT) indicate remission rates to be 10% higher with a 1.0 ms pulse width than with a 0.5 ms pulse width (34). Additional unpublished analyses also indicate that the self-rated overall health status tends to be higher after a longer pulse width stimulus, indicating that any disadvantage in memory disturbance is offset by the better antidepressive effect.

The Swedish national quality register for ECT is the most successful quality register within Swedish psychiatry and the largest quality register regarding ECT in the world. About 90% of patients treated by ECT in Sweden are included in the register. Using the Q-ECT as a base we have included more than 3 500 patients in an ongoing clinical study to identify serum and genetic biomarkers associated with the outcome of ECT. We predict that the use of this register enables the inclusion of the number of patients needed to test the hypothesis.

The investigators have successfully conducted two randomized trials in the field of ECT in recent years, a-study of continuation ECT and a study comparing the effect of ketamine and ECT (35, 36).

Project description

1.1 Type of study:
We plan for a four years national multicenter randomized trial with two parallel groups.

2.1 Inclusion and exclusion criteria

- At least 18 years old at the time of inclusion
- Fulfilled diagnostic criteria for unipolar, or bipolar depressive episode according to ICD-10.
- Has indication for and accepts ECT
- Has a Swedish personal identity number
- Capable of giving informed consent

2.2 Exclusion criteria:

- If the investigator judges a certain pulse width to be inappropriate for the patient.

3.1 Procedure for randomization:
After documented consent, the patient's personal number and hospital are registered in the web-based Q-ECT. This computer-based system presents and records the randomized treatment allocation stratified by hospital and age group.

3.2 Evaluations during the study
Patients can be either hospitalized or ambulant. Clinical and adverse effects will be evaluated and at least weekly evaluations are recommended during the index period (14).

3.3 ECT
The ECT will be performed according to clinical routine, usually three times per week during the index series (14). The anesthetic doses, electrode placement, and stimulus parameters will be adjusted throughout the treatment course, based on seizure quality, clinical improvement, and adverse effects.

Table 1. Information to be collected in the study

	Before ECT (Q-ECT)	1 week after ECT (Q-ECT)	6 months follow-up (Q-ECT)	Other registers after study completion
Indication for ECT	X			
Randomized allocation	X			
MADRS-S	X	X	X	
CPRS-memory	X	X	X	
EQ5D	X	X	X	
ECT treatment		X		
Adverse events		X	X	X
Medication		X	X	X
Diagnoses and admissions				X
Deaths				X
Social factors				X

3.4 Depressive symtoms
Depressive symptoms will be examined by the MADRS-S (37), before ECT, within 1 week after termination of treatment, and at 6 month follow-up. Remission is defined as a score of 10 or less on the MADRS-S. Patients not able to complete the MADRS-S will be rated by the clinician-completed MADRS (38). All patients will also be rated on the Clinical Global Impression Scale (CGI)(39). Antidepressive response (50% reduction on the MADRS-S) will also be reported.

3.5 Quality of life
The EQ5D (40) is used to document the self-rated health status before ECT, within 1 week after treatment termination, and at 6 month follow-up.

3.6 Subjective memory
Patients will be asked to self-rate their level of subjective memory impairment before ECT, within 1 week after treatment termination, and at 6-month follow-up, using the memory item from the CPRS.

3.7 Hospital readmission
After completion of the study, information about previous hospital admissions and hospital admissions during the follow-up period will be collected from the Patient register for statistical analyses.

3.8 Medication
After completion of the study, information about previous psychotropic medication and psychotropic medication administered during the follow-up period will be collected from the Medication register for statistical analyses. Information about medication during ECT will be extracted from the Q-ECT.

3.9 Social factors
After completion of the study, information about education level, employment status, and cohabitation status will be collected from Statistics Sweden for statistical analyses.

3.10 Co-morbidities
After the completion of the study, co-morbidities data will be collected from the Patient register.

4.1 Patients ending their participation in the study

- Patients can choose to end their participation in study activities at any time, including completion of self-assessments; available register data will be used if the patients agree.

5.1 Collection of safety data

The safety of the different ECT dosages will be assessed according to clinical routine. Any adverse events during ECT or within 1 week after ECT will be recorded. Adverse events will also be recorded 6 months after the treatment. Moreover, hospital admissions and diagnosis in ambulant care, as well as causes of deaths, will be collected from the Patient register and Causes of Death register.

6.1 Gains and risks

The potential gains of the study are larger than the risks.
ECT is a safe treatment, recommended for patients with severe depression with or without psychosis, depressed patients with a high suicide risk, and for moderately to severely depressed patients who have not benefitted from other therapies. There is substantial clinical experience with both 0.5 ms and 1.0 ms pulse widths from millions of patients.

This study will generate systematic information on the subjective memory disturbances and antidepressive effects with different pulse widths. Future patients will be treated at the pulse width that produces the more optimal balance between memory disturbances and antidepressive effects.

6.2. Ethical considerations and procedure for informed consent

Patients with depression have a reduced ability to read and process information because of the symptoms of their disease. Ambivalence can be a symptom of severe depression. To ask the patient to make a decision regarding participation in a trial when experiencing severe symptoms of depression is therefore ethically problematic, especially since the nature of the intervention is technical and difficult to comprehend. Some patients have limited insight into their own symptoms and the necessity for treatment. Patients may misinterpret the information on optimal stimulus, exaggerating the risks from ECT, and thereby possibly triggering their withdrawal of consent for ECT. Nevertheless, it is important to include patients with severe symptoms, because such patients tend to have the most benefit from ECT, and optimization of the electrical stimulus during ECT is therefore crucial for this patient group. Another point is that severely depressed patients may find a different balance between antidepressive effect and memory disturbance compared with less severely depressed patients. To solve this ethical dilemma, we will encourage the inclusion of a family member or significant other in the informed consent process and the written information is complemented by individualized oral information. Moreover, the information about the study, including the possibility to withdraw from the study at any time, should be repeated after completion of the treatment series. Then most patients can better process the information and make decisions. The information includes the aim of the study and the procedures, including benefits and risks. The patient will have the opportunity to ask questions. It should be made clear that participation is voluntary, and that it can be terminated at any time without it affecting their future medical care. The consent should include approval to collect information from data sources according to the study requirements, and access to the patient chart for the principal investigator and monitor. The investigator will be able to choose to collect the consent orally or in writing, but regardless of method the consent provided by the patient should be assertive. The consent should be document in the chart prior to randomization.

We are preparing an application for ethics review and no patient will be randomized until the application is approved.

7.1 Statistical analyses

The primary outcome (< 11 on the MADRS-S within 1 week after termination of treatment) will be analyzed using the sample that was randomized and received the intended treatment in the first treatment session (modified intention-to-treat sample). Randomized patients that not receive the intended allocation will be presented, but not included in the primary analysis. If data on MADRS-S and MADRS are missing, remission status will be estimated and imputed according to CGI. The primary outcome will be analyzed using logistic regression in a model including treatment allocation, site, psychosis prior to ECT, age group, and number of antidepressant medications during the last year as independent factors (34). The results of a univariate model including only treatment allocation will also be presented. Stratified results will be presented according to sex, age group, and initial psychosis status. The same model without imputed data will be presented in a sensitivity analysis.

A power analysis indicated that 324 patients are required in each group assuming a 44% remission rate in one group and a 55% remission rate in the other group, a power of 80%, and a double-sided test with alpha of 0.05. Assuming that some patients will not receive the intended allocation, or will be lost to follow-up, we aim to include 400 patients in each group.

The secondary outcome of memory worsening from before ECT to within 1 week after ECT and at 6 month follow-up will be analyzed using repeated measures logistic regression in a model including treatment allocation, site, age group, and sex as independent factors. Stratified results will be presented according to sex and age group.

Self-rated overall health measured with the EQ5D-VAS within 1 week after the treatment series and at 6 month follow-up will be analyzed using repeated measures linear regression in a model with treatment allocation, site and age-group as independent factors. Stratified results will be presented according to sex, age group, and initial psychosis status.

The secondary outcome antidepressive response (reduction of 50% on the MADRS-S) from before ECT to within 1 week after ECT and at 6 month follow-up will be analyzed using repeated measures logistic regression in a model including treatment allocation, site, psychosis prior to ECT, age group, and number of antidepressant medications during the last year as independent factors. Stratified results will be presented according to sex and age-group.

The number of ECTs in the treatment series will be analyzed using repeated measures linear regression in a model including treatment allocation and site as independent factors, and stratified by remission status. Stratified results will be presented according to sex, age-group and initial psychosis status.

Hospital readmission and suicide rates will be presented using the Kaplan–Meier technique, and differences between treatment arms will be analyzed using Cox regression in a model including treatment allocation, site, number of previous hospitalizations, number of antidepressant medications during the last year, and age group as independent factors. Stratified results will be presented according to sex, age group and initial psychosis status.

8.1 Quality control and monitoring
A coordinator/monitor will contact each clinic before the inclusion of the first patient and thereafter when deemed necessary, and at least annually, to insure: that patients are provided information in writing and orally and that consent is documented, assessments are completed and correct, adverse events are reported, original data is saved and that necessary resources are available.

9.1 Data handling
Randomization: The randomized allocations will be stored in the Q-ECT.
Quality register forms: The forms in the Q-ECT will be filled out after the treatment series ends and at 6 month follow-up. Any ECT during the follow-up period will be reported in a new form.
Data enrichment: Statistics Sweden will make a key between the personal identity numbers and serial numbers, and provide the key to each authority that provides data for the study. Region Örebro county will send the data from Q-ECT to the National Board of Health and Welfare. The researchers will be provided with coded data without personal identity numbers.
Statistical analyses: Statistical analyses will be made on coded data.

10.1 Reporting and time frame
Inclusion period: 2019–2022. Statistical analyses and reporting: 2023. The study will be registered at www.clinicaltrials.gov and www.fou.nu.

Equipment
The Q-ECT has access to a web-based system for randomization and data management (INCA).

National collaboration
This research is initiated from the steering committee for the Swedish national quality register for ECT (Q-ECT):
Axel Nordenskjöld, Principal investigator, Registrar Q-ECT, MD, PhD, University hospital Örebro
Niclas Bengtsson, Section chief, Norrland University Hospital
Pär Ejdsäter, Patient association, Balans
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Lars von Knorring, MD, PhD, Professor emeritus, Uppsala University
Mikael Landén, MD, PhD, Professor, Göteborg University
Johan Lundberg, MD, PhD, Psychiatry Stockholm north,
Pia Nordanskog, MD, PhD, Linköping University hospital
Lise-Lotte Risö Bergerlind, MD, Region Västra Götaland

All hospitals that provide ECT in Sweden participate in the quality register.

The study group also involves the prinicipal investigator in the multicenter KETECT-studies that have successfully randomized nearly 200 patients to ECT or Ketamin for the treatment of depression, Pouya Movahed, MD, PhD, Lund University hospital.

Clinical significance
Data from the Q-ECT indicate that remission rates may be approximately 10% higher with a 1.0 ms pulse width than with a 0.5 ms pulse width (36). If these results are confirmed, 400 severely depressed patients who would not otherwise have achieved remission will be relieved of their severe symptoms in Sweden annually. Internationally, thousands of patients could benefit. If remission rates do not differ, adverse events may be reduced.

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