STUDY PROTOCOL

PRASED – Preventing Relapse After Successful Electroconvulsive therapy for Depression

A randomized controlled trial on lithium as add-on to personalized maintenance ECT

V1.6 – 17/04/2019

University of Antwerp - PZ Duffel – UPC KU Leuven – UMC Rotterdam – AZ Sint-Jan Brugge

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1. SUMMARY

Although electroconvulsive therapy (ECT) is a very effective acute treatment for (unipolar as well as bipolar(1,2)) major depression, one of the major challenges in the treatment of mood disorders is to prevent relapse after successful treatment. Without continuation treatment, up to 50% of patients will relapse within 3 months after the last treatment and 6 months relapse rates are as high as 80% (3). Several strategies have been used to decrease these relapse rates. The most commonly used strategy, pharmacological treatment with antidepressants, decrease 6-month relapse rates by 30% (4,5). Nevertheless, as nearly half of patients on antidepressants will relapse within one year after successful ECT, relapse prevention remains a major challenge (6,7).

Other strategies are addition of lithium to antidepressant maintenance treatment or continuation of ECT after the acute course (M-ECT), alone or in combination with antidepressants and/or lithium. These strategies decrease relapse rates to different extents.

In a large RCT, lithium in combination with Nortriptyline reduced 6-month-relapse rates to 32% (8). A recently published audit also found superior results of the combination of an antidepressant with lithium at six months (relapse rate of 16%) (9). Although it is advised to consider lithium combined with an antidepressant as a possible continuation treatment after ECT (10), its effectiveness remains understudied.

M-ECT is a course that begins after the end of the acute ECT course and is intended to prevent relapse of the treated episode occurrence of a new depressive episode (11). Continuation of ECT can be done either at a fixed schedule (slowly tapering of ECT according to a fixed schedule) or personalized (flexible ECT depending on change in the level of depression symptoms). Most studies have used a fixed M-ECT scheme, while clinical practice suggest that a flexible, symptom driven treatment scheme might be more effective in preventing relapse (12). This was confirmed in the recently published PRIDE-study (13). Only 13% of the patients receiving personalized ECT, an antidepressant and lithium had relapsed at six months. This study, however, was limited to elderly patients, who are known to respond better (14) and have a better long-term outcome than the non-elderly (15).

Our project is designed to validate results of the PRIDE-study, not limiting inclusions to older patients, as about half of the patients treated with ECT are non-elderly and relapse prevention in this patient group is as least as challenging. Besides that, we would like to assess the additional effect of lithium addition in preventing relapse with a flexible, symptom-driven and personalized ECT algorithm. After successful brief pulse ECT, patients will be randomized to receive either personalized M-ECT in combination with their ongoing (antidepressant) medication and lithium, or personalized M-ECT in combination with their ongoing (antidepressant) medication without lithium. There will be a follow-up period of one year.

This project enables us to validate the effectiveness of personalized M-ECT, and to assess the effectiveness of lithium as part of a relapse prevention strategy post-ECT. Improving relapse prevention is ‘the most pressing issue in the field’ (7), with an added value for the group of patients with depression that were treated with ECT. As this is only scarcely been investigated, it leaves the clinician without clear guidance on the best treatment strategy after successful ECT. Although our main goal is a positive medical impact, reducing relapse rates eventually also has a socio-economic influence by reducing health care costs.

2. INTRODUCTION AND RATIONALE

2.1. INTRODUCTION

As mentioned before, one of the major challenges in the treatment of mood disorders with ECT is to prevent relapse after a successful acute course. Although relapse prevention strategies have been investigated in several studies, current guidelines offer only a limited amount of information to clinicians regarding the best form of continuation treatment. Withholding continuation therapy results in relapse rates of up to 80% within 6 months after the last treatment (3–5). Jelovac et al. conclude that the risk of relapse in the year following ECT is substantial, with the first 6 month-period encompassing the greatest risk for relapse (3).

The now most commonly prescribed form of continuation treatment are antidepressants, lowering 6month relapse rates by 30% (4,5). However, 50% of patients will relapse within one year, the majority in the first six months (37%). The largest evidence base for efficacy in post-ECT relapse prevention exists for the tricyclic antidepressants. Other strategies used are addition of lithium to antidepressant maintenance treatment or continuation of ECT after the acute course (M-ECT), alone or in combination with antidepressants and/or lithium. These strategies decrease relapse rates to different extents.

Regarding ECT, guidelines about continuation of therapy remain scarce whereas regarding antidepressants, all guidelines recommend a continuation regimen for one year or longer after remission has been achieved. This implicates that ECT often is stopped when remission is achieved, instead of continuing at a lower frequency. Given the limited effectiveness of current continuation treatment protocols, researchers have been looking for alternatives, with following strategies being most promising:

Lithium

The first promising alternative is combination of lithium with a given continuation treatment (ECT or antidepressants) following an acute ECT course. In a large RCT, lithium in combination with nortriptyline reduced 6-month-relapse rates to 32% (8). A recently published audit also found superior results of the combination of an antidepressant with lithium at six months (relapse rate of 16%) (9). Other studies show promising results but are not as hopeful as the before mentioned studies.

A study conducted in the USA compared two maintenance treatment schemes: monotherapy with tricyclic antidepressants (TCA) on the one hand, and combination therapy of TCA-lithium on the other hand (16). Patients were randomly assigned to receive continuation treatment for 24 weeks with placebo (n = 29), nortriptyline (n = 27) or the combination of nortriptyline and lithium (n = 28). The study indicates that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT (84%). Monotherapy with nortriptyline has limited efficacy (60% relapse rate). The combination of nortriptyline and lithium is more effective (39% relapse), but the relapse rate is still high, particularly during the first month of continuation therapy.

A rather large study (N=122) by Prudic e.a. (17) compared maintentance pharmacotherapy of two combination schemes: nortriptyline-lithium and venlafaxine-lithium. No difference in relapse rate (both had relapse rates of 50%) or adverse effects was detected between the treatment schemes.

All literature on lithium as a prophylactic against depressive relapse after ECT has recently been reviewed (10). Rasmussen e.a. concluded that there is strong evidence that lithium can help prevent relapses in the first 6 months after successful ECT. However, there are several unanswered questions about its use post-ECT such as the optimal duration of use, and concomitant antidepressant choice.

M-ECT

M-ECT is a course that begins after the end of the acute ECT course and is intended to prevent relapse of the treated episode occurrence of a new depressive episode (11). Continuation of ECT can be done either at a fixed schedule (gradual tapering of ECT according to a fixed schedule) or personalized (flexible ECT depending on change in depression symptoms) and starts to find its way into daily clinical practice.

Within this context, a Swedish study compared pharmacological continuation treatment with a combination of pharmacotherapy and M-ECT (N=56) (18). In addition, all patients were offered augmentation with lithium. The post-ECT relapse rates were substantial in both treatment groups with a statistically significant advantage, i.e. lower relapse rates, for combination of pharmacotherapy and continuation ECT. Moreover, patients on lithium showed significantly lower relapse rates than the nonlithium group.

M-ECT (10 treatments) was also directly compared to efficacy of lithium plus nortriptyline (6 months) (8) by the CORE Consortium for Research in Electroconvulsive Therapy. They concluded that both treatment strategies were equally effective and superior to a historical placebo control group, but both had limited efficacy with more than half of patients either experiencing disease relapse or dropping out of the study (M-ECT group 37% relapse, 17% dropout, lithium + nortriptyline 32% relapse, 22% dropout). The authors concluded that more effective methods to prevent relapse are needed.

Most studies have used a fixed M-ECT scheme, while clinical practice suggest that a flexible, symptom driven treatment scheme might be more effective in preventing relapse (12). To improve relapse rates, Odeberg e.a. (19) introduced individually tapered M-ECT with concomitant medication after an acute course of ECT. The mean duration of administered continuation ECT at follow-up was 1 year, but for most patients (63%), ECT had been terminated after the acute course. For 49% of patients, adjustments between ECT sessions had been made due to early signs of relapse. Two weeks was the most common interval between sessions for patients with ongoing ECT. The need for hospital care 3 years before and after the initiation of maintenance ECT + medication was evaluated. The number of patients hospitalized, number of admissions, and total days in hospital were all significantly reduced. Hospital days were reduced by 76%. This study presents the evidence that supports previous findings that individually tapered ECT combined with medication can maintain initial response to ECT and serve as a bridge to long-term relapse prevention.

As there was no clear adjustment scheme in the study done by Odeberg e.a., it is hard to confirm their results. Lisanby e.a. (12) proposed Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE) as a novel patient-focused approach to perzonalize the ECT schedule. In STABLE, the ECT schedule adapts to symptom fluctuations to prevent over-treatment of those who do not need it, and to re-capture response in those who might have otherwise relapsed with a rigid dosing schedule. It has taken several years to test this algorithm in an RCT but results of treatment according to the STABLE algorithm in an elderly population were published a few months ago in the PRIDE study (13). The algorithm proved to be very effective with only 13% of relapse in the personalized ECT plus medication (Venlafaxine + Lithium) group at six months. The group that was treated with (the same) medication, e.a. Venlafaxine + Lithium, had 20% relapse at six months. This study, however, was limited to elderly patients, who are known to respond better (14) and have a better long-term outcome than non-elderly (15). Another difference with ECT practice in Belgium is that the USA study used ultra-brief pulse ECT. This is a treatment method well tolerated but not as effective (20) as brief pulse ECT that is used for our acute and continuation treatment schedules. Besides that, they were treated with venlafaxine and not with a TCA. It can however be concluded that additional ECT after remission (only as needed) was beneficial in sustaining mood improvement for most patients.

Literature on M-ECT was also reviewed a few years ago (21). The conclusion was that maintenance ECT was efficacious for the prevention of relapse of major depression and that the efficacy increased when combined with antidepressant medication and at flexible treatment intervals, responsive to early signs of recurrence.

To conclude, there is a substantive amount of evidence for a role of antidepressants in relapse prevention after an ECT course. Tricyclic antidepressants and Venlafaxine seem to be promising antidepressants and can contribute to sustaining remission after successful ECT. As this is often not sufficient to retain remission of prevent recurrence of a new depressive episode, a symptom driven form of continuation ECT and addition of lithium to the treatment can be considered as potential strategies to improve treatment after successful ECT. Confirmation of their potential in a depressed sample of all ages has never been done and would be valuable.

2.2. RATIONALE

Although electroconvulsive therapy (ECT) is a very effective acute treatment for depression, one of the major challenges in the treatment of mood disorders is to prevent relapse after successful treatment. Several strategies have been used to reduce relapse rates but most of them seem to be relatively unsuccessful. We selected the two strategies that we consider to be least investigated and most promising in relapse prevention. An RCT was designed to determine their potential to reduce relapse after successful ECT.

3. OBJECTIVES

The present project is designed to study two promising relapse prevention strategies in an RCT. This will be the first project worldwide to study the effects of a personalized ECT treatment algorithm in the continuation phase of depression in an ECT-responsive population of all ages. The project holds promise for diminishing relapse rates after successful ECT, thereby being of potential impact for a vulnerable group of patients with an often-recurring form of major depressive disorder. The underinvestigated role of lithium after successful ECT is the focus of our project. In order to improve implementation options, we assess self-rating of mood alongside clinician-ratings.
To investigate the effectiveness of these strategies, a multidisciplinary research project with partners from UAntwerp as well as PZ Duffel, KULeuven, AZ Sint-Jan in Brugge and our Dutch partner UMC Rotterdam was set up. With the expertise, skills and patients available at the consortium participants, the research team will be able to address the challenges of the project in terms of planning and organization of the treatment and testings. This is a completely clinical study with the intent to decrease relapse rates after successful ECT. The concrete scientific objectives (SO) will be the following:

- SO1: Investigate the additive effect of lithium-addition to symptom-driven M-ECT and antidepressant treatment in preventing relapse after successful ECT.
- SO2: Validate the effectiveness of a personalized, symptom-driven approach of maintenance ECT (for 6 months) in depressive patients that have responded to an acute ECT-course.
- SO3: Compare clinician-rated mood with scores on self-rating scales.
- SO4: Evaluate the tolerability of combined continuation treatment in the two different treatment arms by assessment of cognitive functioning.

4. Study Design

All patients that respond well to treatment with ECT for unipolar depression in one of the four treatment centers, are screened for eligibility in the study. Patients that have reached the remission criterion (strict (IDS-C ≤ 12) or liberal (IDS-C ≤ 17) on two consecutive measurements) after this ECT course are considered eligible to participate in this RCT. Retrospectively, the pre-treatment depression characteristics are evaluated because the presence of a unipolar depressive disorder (MINI International Neuropsychiatric Interview) of at least moderate severity (IDS ≥ 29) at baseline is necessary for inclusion in the study. Furthermore, they have to be treated with either tricyclic antidepressants or venlafaxine.

When patients provide their written informed consent for the study, phase 1 starts - open label antidepressants are continued and personalized ECT (see Figure 1) is given for the next six months. Patients will be randomized to addition of lithium or no lithium.

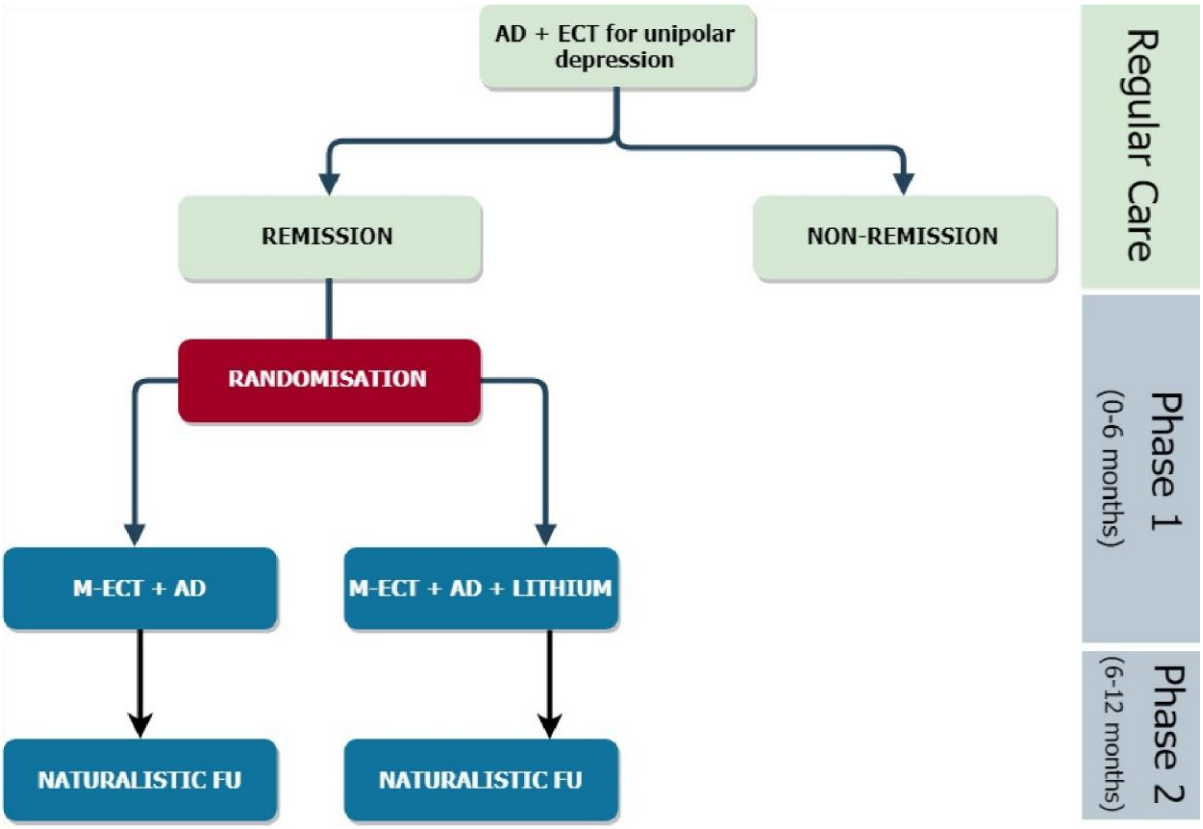

Figure 1 - PRASED study design. ECT = Electroconvulsive therapy; AD = antidepressants.

Personalized ECT in the maintenance phase of the treatment is given according to the so-called STABLEalgorithm (Symptom-Titrated Algorithm-Based Longitudinal ECT, (Table 1) that was translated to a version that can be used with the Inventory of Depressive Symptoms (IDS), the depression severity scale that we use in our study instead of the HDRS24 on which the STABLE-algorithm was originally based. Scores were changed in to the IDS-equivalents of the HDRS24-scores (22,23).

Table 1 - Symptom-Titrated Algorithm-Based Longitudinal ECT – translated to IDS-C

Weeks 1–4: Fixed ECT schedule		
One treatment 2–5 days after randomization, one treatment 7–12 days after randomization, one treatment 14– 19 days after randomization, and one treatment 23–28 days after randomization (a total of four ECT treatments in 1 month)		
Weeks 5–26: Symptom-Driven ECT Schedule		
N° Additional ECTs	IDS-C conditions	Relapse potential
0	Current IDS-C score ≤9 Current IDS-C score 10-13 and previous score was 7-13 and current score is ≤ 2 points higher than previous score Current IDS-C score 10-17 and ≤ 2 points higher than baseline score	Low
1	Current IDS-C score intermediate between criteria for low or high relapse potential	Moderate
2	Current IDS-C score ≥22 Current IDS-C score 14-21 and current score is ≥ 3 points higher than previous score and current score is ≥ 9 points higher than baseline score	High

After six months, phase 1 ends and patients enter phase 2 of the study. In this phase, we no longer control treatment. Care will be handed over to the treating psychiatrist. In consultation with the patient, treatment with lithium can be continued and there is a possibility to continue M-ECT when this seems beneficial for the patient. In phase 2, mood and (change in) treatment of the previous three months will be assessed at 9 and 12 months after randomization.

The design of the PRIDE study (13) was used to inspire our protocol, although the treatment arms we compare are somewhat different. Adaptations were made according to European ECT practices and feasibility in our centers.

5. Study Population

5.1. Patient recruitment strategy

Before starting treatment with ECT, patients for whom a course of ECT is indicated will routinely undergo a diagnostic workup. As part of this diagnostic workup, a MINI diagnostic interview is done and when a unipolar major depression diagnosis is confirmed by this interview, patients will be considered eligible for the PRASED-study. After an acute course of ECT with antidepressants (TCA dosed according to target plasma level or venlafaxine (target dose of ≥ 225mg/day)), patients will be screened for eligibility, depending on whether or not they reached remission after treatment with ECT. The research team will be notified when the last treatments of the acute course are planned. In the last week of the acute treatment, mood is evaluated and when remission is confirmed, patients will be

informed about the PRASED study. When remission is confirmed one week later, informed consent for the PRASED study will be asked.

5.2. Inclusion and exclusion criteria

Patients will be recruited in the four participating clinics. After having been informed about the study procedures, patients are asked to sign the informed consent form. The in- and exclusion criteria will be evaluated to decide whether or not the patient can participate.

Inclusion criteria:

- Major depressive disorder patients
- Treatment with either an adequately dosed TCA (with therapeutic blood levels) or venlafaxine (target dose of ≥ 225mg/day)
- Remitted (IDS-C≤17) after an acute course of ECT
- Age 18 or older
- If applicable, use of appropriate contraception.

Exclusion criteria:

- Patients with bipolar, schizoaffective disorder or schizophrenia
- Patients already being treated with Lithium, or with a contra-indication for its use
- Patients with documented dementia or intellectual disability - Substance abuse or dependence in the past 6 months - Pregnancy or breastfeeding.

5.3. Power analysis

For the power-analysis, we have looked at the relapse rates in two studies. The first one compared antidepressant maintenance treatment with a TCA with TCA+lithium (16) – with respectively 60% and 39% relapse after 24 weeks. The second one was the PRIDE study (13), that compared antidepressants+lithium with antidepressants+lithium and the personalized M-ECT according to the STABLE-algorithm, the proportion of relapse in this study was remarkably lower (20 vs 13%), possibly due to the fact that the treated patients were elderly and that M-ECT was additionally used in the group with the lowest relapse rate. Based on our study design and targeted study population (not only elderly), we expect relapse rates to be somewhere in between those of the two studies.

As we consider a difference in relapse rates of 15% between the groups clinically relevant, our power calculation was done using relapse rates of 15% in the one treatment arm and 30% in the other one. We did a power calculation with an α of 0.05 and a standard power value of 0.8. With a sampling ratio of 1 (the same number of patients in the two groups), we would need a sample size of 95 in each group for our primary outcome measure. That makes a total of 190 patients.

Because of the intensity of the study protocol (weekly evaluation of mood), we some dropout and aim at inclusion of 240 patients at randomization so that a dropout of 20% would leave enough patients to do meaningful statistical analyses at the start of phase 2 (after 6 months) of the study. Given the size of the ECT units, we expect to randomize 88 patients in Leuven, 64 in Duffel, 64 in Brugge and 24 in Rotterdam.

6. Treatment of patients

6.1. Antidepressants

Patients are eligible for participation in the study when they are treated with either an adequately dosed TCA (with therapeutic blood levels) or venlafaxine (target dose of ≥ 225mg/day) at the start of the study. Antidepressant treatment is continued throughout phase 1 of the study study.

6.2. ECT

6.2.1. Acute phase – Treatment-as-usual

All patients sign a general ECT informed consent, as routinely used in daily clinical practice, before treatment with ECT is initiated, stating that they agree with the suggested treatment and where they can indicate that routinely collected data during treatment can be used for research purposes to improve ECT practice.

Patients are treated twice a week, with standard right unilateral electrode placement (RUL) (d'Elia placement) using either a Somatics Thymatron System IV (Somatics, Lake Bluff, Ill.) or a MECTA spECTrum device (MECTA Corporation, Portland, Ore.) with a pulse width of 0.5 ms (or higher if needed). A dose titration procedure (see appendix * dose titration) to determine seizure threshold (ST) is conducted at the initial treatment and subsequent treatments are administered at six times the ST. Stimulus dose is raised by first maximizing train duration, followed by increase of frequency, and increase of pulse width, using a constant current (0,8 A). Motor seizure duration is evaluated at sight or with the cuff-method, and two channels of EEG (frontal-mastoid) are recorded.

If the IDS score demonstrates a decrease < 25% from baseline by treatment 6, the stimulus dose will be increased by 50% at the 7th session. If the IDS-C score demonstrated a decrease <25% from baseline by treatment 9, the stimulus dose will be increased again by 50% or a switch to bitemporal ECT can be chosen, with empirical dose titration and subsequent treatments administered at two times ST (Figure 2).

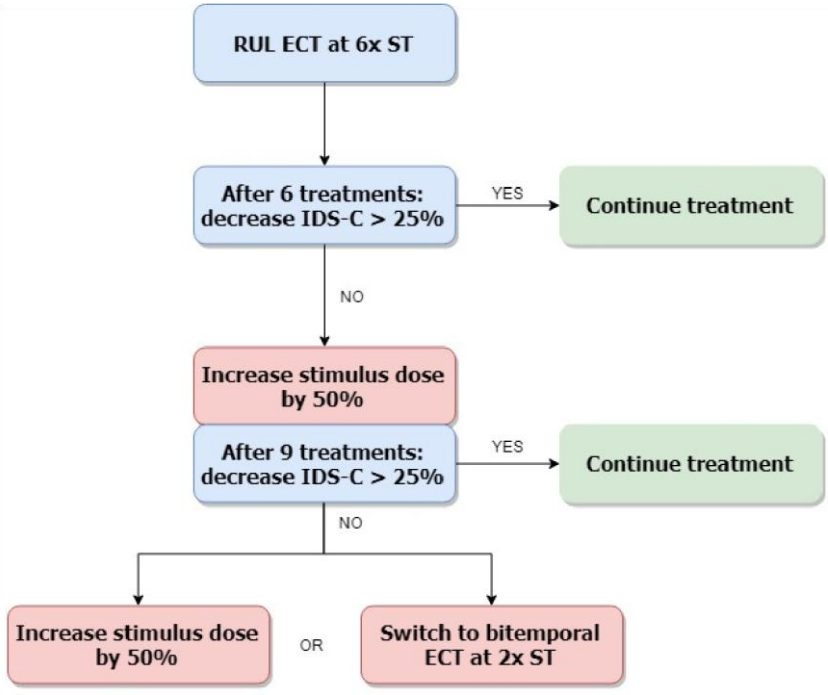

Figure 2 - ECT treatment schedule - acute phase

ECT was continued until patients achieved remission or had a plateau. Treatment with ECT is ended when patients show no improvement at all after 10 sessions of BT ECT.

Anesthetic medications consist of propofol (1mg/kg) or etomidate (0.2mg/kg), and succinylcholine (1.0 mg/kg), given intravenously. ECT was continued until patients achieved remission or had a plateau in improvement over at least two consecutive evaluations.

As part or regular care, cognitive functioning is also evaluated at baseline and after the acute treatment course.

6.2.2. After successful ECT (start PRASED)

Patients who have achieved remission, confirmed after one week, during acute treatment with ECT (treatment as usual) are eligible to participate in PRASED. After signing informed consent patients continue with personalised M-ECT according to the STABLE algorithm and are randomized to either receive lithium or not. The stimulus dose of the acute ECT course is continued in the continuation phase. After 4 weekly treatment sessions, the frequency of ECT-sessions is determined on the basis of symptom severity as assessed by the patient's IDS scores-C (Table 1) (weeks 5–26). In phase 2 of the study (weeks 27-52), treatment is continued by the treating psychiatrist who decides whether or not ECT, lithium and antidepressants are to be continued or stopped.

Patients visit the clinic twice a month to evaluate mood and supplemental IDS-C telephone screenings will be done in the alternating weeks. When telephone IDS-C scores increased significantly based on the STABLE algorithm criteria for moderate to high relapse potential, the patient will be scheduled for an interim confirmatory clinical evaluation within 48 hours. Treatment decision will be based on the clinical confirmation IDS-C.

As in the PRIDE study (13), the data centers will enter their results in a web-based program that collects the results for both clinical and telephone visits. The study coordinators at the different study sites will be provided with a description of the appropriate action (plan ECT sessions, schedule interim clinic visit if telephone IDS-C is significantly increased, plan next telephone or clinic visit).

The study will be discontinued if the patient no longer wants to participate or in case of adverse events that raise safety concerns.

6.3. Lithium

Patients in the Lithium-arm will also be treated with antidepressants and M-ECT. Additionally, openlabel lithium will generally be started at 400 mg/day, or lower in older patients. Lithium will be used in moderate doses with a target blood level 0.5–0.7 mEq/L. The day before ECT, the evening dose of lithium will be withheld. On ECT-days, lithium levels will be measured. Lithium levels will also be obtained at weeks 2, 3 and 4 weeks 8 and every 4 weeks after that. TSH and creatinine will be checked at 4, 12 and 24 weeks. Medication changes will be made on the basis of blood levels and clinical side effects.

The schedule of patient contacts for clinical and telephone ratings is identical to the schedule in the treatment arm without lithium.

7. METHODS

Many tests are part of standard care and will be done once signed up for ECT. Retrospectively, eligibility based on diagnosis and severity of depression before start of ECT will be assessed. The extra assessments in the light of this study are situated after patients remitted after treatment with

ECT. The participants are of course allowed to object any or part of the assessments. The time schedule of the project can be found in section 0.

Of each patient scheduled for treatment with ECT, several standard variables are registered:

- Age
- Gender
- Educational level - Episode duration
- Presence of psychotic features
- CORE-defined melancholic features
- Baseline IDS-values
- Number of previous episodes
- ECT-appropriateness Scale (severity, heritability, episodic nature) (24)
- Maudsley Staging Method

7.1. Treatment parameters

Treatment parameters of each treatment with ECT are registered. Data on electrode placement, stimulus dose, use of anesthetic, muscle relaxant and insult characteristics are stored in the ECT-files.

7.2. Treatment effect

The severity of depression (primary outcome) will be tested with the IDS-C (Inventory of Depressive Symptomatology - Clinician) at twice-monthly clinic visits. Self-rating with the IDS-SR (Inventory of Depressive Symptomatology – Self-rating) will also be done once a month at one of the clinic visits. The weeks in between, a telephonic IDS-C will be done. Psychotic symptoms will be assessed with the Psychotic Depression Assessment Scale (PDAS)(25,26) once every month at a clinic visit.

We can only aim at an independent assessment of mood (without knowledge of the treatment arm) but realize that the blinding will not be complete when for example Lithium side effect are mentioned by a patient during evaluation of mood.

7.3. Side effects

As part of standard clinical care, cognitive functioning is assessed at baseline and after the acute ECT course. For this study, an assessment of cognitive functioning will also be done 1 and 6 months after patients remitted.

The cognitive testing battery is comprised of several tests sensitive to the effect of ECT and lithium (27). To measure global cognitive functioning, the Montreal Cognitive Assessment (MOCA) (28–30) will be done once monthly at the clinic visits. The Controlled Oral Word Association Test (COWAT), a test for verbal fluency very sensitive to the effects of ECT as well as Lithium is added to this monthly measurement of global cognitive functioning. We will alternate between three different versions of the MOCA and COWAT, to diminish potential learning effects.

At baseline, after the acute ECT course and at 1 and 6 months after the acute course the complete cognitive battery is completed:

Acute postictal confusion	Time to orientation after ECT (name/age/date of birth/day of week/place).	
General cognitive functioning	Montreal Cognitive Assessment (MOCA)	15min

Attention	Trail-making test – A (TMT-A)	7min
Executive functioning	Trail-making test – B (TMT-B)	
Verbal memory	Rey Auditory Verbal Learning Test (RAVLT)	5 min
Verbal fluency	Controlled Oral Word Association Test (COWAT)	3min
Autobiographical memory	*Kopelman Autobiographical Memory Interview*	*30 min**
Subjective functioning	Subjective Assessment of Memory Impairment (SAMI)	1min

* In the two smaller recruitment centers (Brugge and Rotterdam), the test battery will be done without the test for autobiographical memory to improve feasibility.

Other adverse events and serious adverse events will be summarized by number of patients experiencing the event and relatedness to study interventions.
An electrocardiogram (ECG) will be applied as a standard procedure in the context of ECT and lithium administration. In case of an abnormal ECG, further cardiological examinations will be performed by the cardiologist before starting ECT and/or lithium treatment.

7.4. Randomisation and treatment allocation

After inclusion (e.g. remission after a successful course of ECT), the randomized controlled trial starts. Randomization to either the treatment arm with lithium or the one without, will be done by the study coordinator, per center.

8. Time Schedule

	Regular care					Trial Phase 1 0-26 wks						Trial Phase 2 27-52 wks
	Before acute course	Each ECT	After 6x ECT	After 9x ECT	After acute course	Weekly	After 1 month	Monthly	After 6 months	At 2, 3, 4, 8, 12, 16, 20, 24 weeks	Each ECT	Every 3 months
Sociodemographics	X											
Diagnostics	X											
Clinical characteristics												
IDS-CR	X		X	X	X	X						X
IDS-SR	X				X			X				X
PDAS	X				X			X				
CORE	X											
Cognition												
Postictal confusion		X										
MOCA	X		X		X		X	X	X			
TMT-A	X				X		X		X			
TMT-B	X				X		X		X			
RAVLT	X				X		X		X			

COWAT	X		X		X		X	X	X			
AMI	X				X		X		X			
SAMI	X				X		X		X			
Blood Li (+ TSH + creatinine)										X	X	
Treatment characteristics		X									X	

Table 2 - PRASED time-schedule

9. STATISTICAL ANALYSIS

9.1. Outcome measures

The IDS-C will be measured longitudinally over the first treatment phase of 6 months. The effect of treatment arms will be compared during and at the end of these 6 months. As a primary outcome measure, comparing the lithium-arm with the arm without lithium, we look at the time-to-relapse and time-to-event (both measured in days from randomization), with the event being additional ECT given according to the STABLE algorithm. Patients will be categorized as having relapsed when 2 consecutive IDS-C measurements are ≥29, when they require psychiatric hospitalization or are acutely suicidal (IDS-C score of 3 on suicide item). Dates of treatment and assessments therefore have to be carefully recorded.

At the end of phase 1, the relapse status will also be evaluated. Besides that, the severity of depressive symptoms at endpoint will be compared between the treatment arms and the total number of ECTs during phase 1 of the study will be compared between the two treatment arms.

Secondary analyses of IDS-C scores will focus on the IDS-C trajectory over the study period. Another efficacy outcome is the self-rated mood (IDS-SR).

All patients included in the study (randomized), will also be included in the data analysis, irrespective of the adherence to the treatment or dropout. This analysis method offers a more accurate, unbiased estimate of the effectiveness of the therapy than that yielded from a per-protocol or as-treated type of analysis.

9.2. Analyses

The study sample will be described by frequency distributions for categorical variables and means with standard deviations for continuous variables (using parametric or nonparametric tests depending on the required model assumptions). Time-to-event and time-to-relapse will be evaluated in a survival analysis. Subjects who did not relapse at the end of the study (six months after randomization) will be censored. The comparison of relapse between the two treatment arms will be accomplished comparing odds ratios. The severity of depressive symptoms between the groups will be compared by independent t-tests. Comparison of the number of ECT sessions in phase one of the study will by done using Poisson regression models. The evolution of depressive symptoms during the study will be evaluated using linear mixed models.

10. ETHICAL CONSIDERATIONS

10.1. Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki.

10.2. Recruitment and consent

All patients that undergo ECT will sign an informed consent form for this treatment, as already applied in daily clinical practice. At this form, they can indicate if the routinely collected data during treatment can be used for research. All patients that agree with this statement will retrospectively be screened for eligibility for the study and when remitted, informed about the study, including the procedures, and potential individual benefits and personal risks. The patient information brochure and informed consent form are presented. The patient is granted at least one week time to decide (with partner or family members) whether or not he or she wants to participate. When the patient wants to participate, the informed consent form has to be signed. The informed consent can be withdrawn at any time during the study without consequences for further treatment.

10.3. Fees

As the study implies a weekly evaluation of mood and therefore 2-weekly visits to one of the treatment centres, patients will be reimbursed for their travel expenses for visits related to the study. Transportation to the ECT-unit on a treatment day will be at their own expense.

11. Data management plan

All general patient and treatment characteristics are assessed and stored in the study files on the ECT ward. The other data collected in the light of this project are questionnaires on patient mood and cognition and self-rating scales. Rating will be done by raters not aware of the allocated treatment arm. Besides rating scales, blood samples will be drawn to determine plasma levels of antidepressant / lithium treatment. Results of blood sampling will also be stored in the study files. Details on ECT and pharmacological treatment will be stored in the general ECT files.

The person responsible for data preservation is the key investigator Didier Schrijvers. All acquired data will be entered at a data platform that will allow safe data storage and processing from the different study sites. Employees of the project will be granted permission to input data depending on their role in the project. Data will be stored for 15 years after study completion in the database and in study files. We choose to extend data storage to 15 years to allow secondary analyses on the acquired data after publication of the first results.

To make sure that the privacy of participants of the study is guaranteed, their data will be processed anonymized. At study entry, a study number will be assigned and data entered in the data platform will only have this study number and no other details that could enable identification of the patient based on these details. The study files that do contain name and contact data of the patients will be stored in a locked closet at the ECT units.

12. Composition of the Project Team

By uniting several research groups, we create a consortium with an adequate amount of expertise and eligible patients to make this a successful project. The research consortium will meet every month until first inclusion and every three months afterwards to discuss study and scientific progress. The advisory board will also meet regularly.

Principal Investigator/PI:	Dr. D. Schrijvers, psychiatrist, PZ Duffel, UAntwerpen
Coordinating investigator:	Dr. L. Van Diermen, psychiatrist, UAntwerpen

Project members:	Prof. Dr. P. Sienaert, psychiatrist, UPC KU Leuven
	Dr. T. Birkenhäger, psychiatrist, Erasmus MC Rotterdam (NL)
	Dr. H. van den Ameele, psychiatrist, AZ Sint-Jan Brugge
	Dr. B. Vlieghe, psychiatrist, AZ Sint-Jan Brugge
	Dr. E. Poljac, PhD, study coordinator, UAntwerpen
	Dr. J-B. Belge, MD, UAntwerpen
	Dr. S. Lambrichts, MD, UPC KU Leuven
	Dr. K. Vansteelandt, PhD, UPC KU Leuven

To create a multidisciplinary team, each center will recruit or reassign two employees: one responsible for local ECT- and study planning and coordination, preferably already part of the ECT-team at the designated center. The other employee will be a psychological assistant or trainee psychiatrist responsible for testing. The whole project will be supervised by a study-coordinator overseeing startup and progress of the project at the 4 centers.

- Study coordinator will be in touch with the core project members to report about progress and problems at the different study sites.
- 2 PhDs (Duffel / Leuven): responsible for assessment of mood, will be supervised by local supervisors on a weekly basis.
- Psychological assistant: responsible for cognitive assessment and assessment of mood.
- Study nurse: responsible for ECT-planning and communication, blood sampling for patients in the lithium treatment arm.

The executive staff will regularly schedule so-called mood- and cognitive- sessions with the testers of all participating centres to align scoring of depression severity and cognitive functioning. After finalization of the project, the co-supervisors of the consortium will support analyses of the results by the PhD-researchers and implement study results in daily clinical practice.

13. Feasibility

The study will be coordinated by the University of Antwerp, with patient recruitment at four clinical ECT-units situated in mental health care institutes. Inclusion centers are 1) University Psychiatric Hospital Duffel, 2) UPC KU Leuven 3) AZ Sint-Jan Brugge and 4) UMC Rotterdam in The Netherlands. The study will be registered at clinicaltrials.gov.

The study protocol has now been finalized and a script for the study is in preparation. A web-based coordination system for implementation of the STABLE-algorithm and online data platform is set up. Study protocols will be submitted to the four respective medical-ethical boards. Data collection will start after approval of all medical-ethical boards is obtained. Gross of this work and coordination of this work package will be done by the project team and the study coordinator who has recently been appointed at the University of Antwerp in collaboration with the local co-supervisors of the four inclusion sites.

The start of the PRASED-study is estimated the 1st of March 2019 at all four sites and we hope to reach the inclusion target at the end of September 2021. We hope to complete phase 1 of the project at the end of April 2022. As we have planned follow-up meetings (at 9 and 12 months) with patients that were treated in one of the two treatment arms, last data will be collected in October 2022 (Table

3). In the last phase of the study, analyses will be started and published in collaboration with the four centres. Implementation of the results to be used in clinical practice will be the last step of this project.

	2018				*2019*				*2020*				*2021*				*2022*			
	Q1	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*
Study preparation																				
Data collection Phase 1																				
Data collection Phase 2																				
Analyses and writing																				→
Implementation																				→

Table 3 - Overview of planning of work packages

14. Potential obstacles

A potential obstacle would be gaining informed consent from the patients. Although the treatment is usually very effective, we noticed in earlier projects that some of the patients develop fear for treatment and as a consequence are relieved that the acute treatment course ended. It is possible that, although informed of the possibility that quick relapse is not unusual, patients will refuse a rather intensive follow up after successful ECT and participation in the study. This could hamper inclusion rates. Correct education of the patients to increase awareness of the risk of a sudden cessation of ECT after a successful course and involving the family could help to tackle this potential obstacle.

Besides willingness to be that closely followed, there might also be more practical obstacles. Some patients have to drive more than 30 minutes for evaluation of their mood or and ECT treatment. The older part of our population might therefore require extra effort of caregivers and/or the team to accomplish adherence to the treatment algorithm.

15. SAFETY REPORTING

15.1. Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to treatment with antidepressants, ECT or Lithium. All adverse events reported spontaneously by the subject or observed by one of the investigators will be recorded.

The AEs are graded by the investigator on a three-point scale as defined below:

Mild	Discomfort, not affecting daily activity
Moderate	Discomfort, affecting daily activity
Severe	Inability to perform daily activity

For each adverse event the relationship to the study as judged by the investigator as well as eventual actions taken will be recorded.

15.2. Serious adverse events (SAEs)

A serious adverse event is any medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

15.3. Reporting of adverse events

All adverse events during the study will be reported (screening until one month after completion of the study (52 weeks after randomization). The main investigator will report all SAEs to the Medical Ethics Review Board that approved the study (Universitair Ziekenhuis Antwerpen) electronically (email: ethisch.comite@uza.be). All SAEs will also be recorded and reported to FAGG using the European form (https://www.famhp.be/sites/default/files/downloads/sae_reporting_form_en.xlsx).

15.4. Liability insurance

Liability insurance for this project has been taken out with Amlin Insurance SE, providing cover for damage to research participants through any injury caused by the study (no-fault insurance according to art. 29 of the Law Experiments on the Human Subjects dated 07/05/2004).

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Appendix Dose Titration

EMPIRISCHE DOSISTITRATIE

Drempelbepaling
(ULTRA)BRIEF - BT/BF/RUL

Dose level	%	Charge (mC)
1	**5**	25
2	**10**	50
3	**15**	76
4	**25**	126
5	**35**	176
6	**50**	252
7	**70**	353
8	**100**	504

BT drempel x 2
RUL drempel x 6

ect titratie procedure Prased