Prediction of ECT treatment response and reduction of Cognitive Side-effects using EEG and Rivastigmine

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This study has been transitioned to CTIS with ID 2024-518047-37-01 check the CTIS register for the current data. The aim of our study is two folded: first, we aim to improve cognition after ECT, improving its acceptability and tolerability and hence...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54344

Source
ToetsingOnline

Brief title
PRECISER

Condition

- Other condition
- Mood disorders and disturbances NEC

Synonym
Depression

Health condition

Cognitieve stoornissen

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: NWO (ZonMw)

Intervention

Keyword: EEG, Electroconvulsive therapy, Rivastigmine, Side-effects

Outcome measures

Primary outcome

Main outcome is change in cognitive performance in three domains between baseline (max. 1 week before the first ECT session) and end of treatment (max. 1 week after the last ECT session). Since cognition comprises different and (largely) independent domains, three different tests assessing different cognitive domains will be main outcomes: verbal memory and learning, verbal fluency and general cognition. These cognitive domains have been shown to be most affected by ECT in our previous work, and recommended by international consensus. We will use three (sub)tests that yield individual standardized scores (based on comprehensive norm groups). Patients receiving ECT showed a significant decline in cognition on these (sub)tests:

1. Dutch adaptation of the Rey Auditory Verbal Learning Test (D-RAVLT; 15 words test): assessing verbal learning and memory. We use the subtest called *delayed recall* as primary outcome variable for this domain. This subtest counts the number of words a participant can correctly recall from a list of words presented 20 minutes earlier.

2. Verbal fluency (the letter N, A, and categorical fluency): assessing verbal fluency. We use the categorical subtest as primary outcome for this domain. This test counts the number of words a participant can produce in one minute from a certain category (e.g. professions or animals). Furthermore, responses to the letter *N* and *A* will be counted.

3. Montreal Cognitive Assessment: the MoCA yields a score that reflects overall cognitive functioning. Different domains (visual, verbal, memory) are tested. The test will take 10-15 minutes.

Efficacy of ECT on depressive symptom severity will be assessed with the Hamilton Depression Rating Scale (HAM-D), as part of standard clinical practice. Regarding the outcome prediction algorithm, the accuracy of the prediction model will be used as primary outcome measure, with specificity for non-response and non-remission (defined based on the HAM-D scores) as secondary outcome measures.

Columbia University Autobiographical Memory Interview (CUAMI), short form
The CUAMI is specifically tailored to measure autobiographical memory deficits resulting from ECT. As such, it is also recommended by the GEMRIC consortium as valid measurement instrument of autobiographical memory. We decided to include the short form version in this study to minimize the burden on patients. The CUAMI short form, takes about 30 minutes to complete.

Secondary outcome

Electroencephalograpy (EEG)

EEG recordings will be performed with BioSemi hardware (Amsterdam, The Netherlands) using a cap with 64 active electrodes, sample frequency 2048 Hz. Patients will be lying down and instructed to lay still with their eyes closed. Resting state recordings will be obtained during 18 minutes. After the resting state recording, an additional recording of a test battery will be applied. A portable BioSemi recording device will be used in all participating centers to ensure standardization of data acquisition. Patients will start with resting state EEG recordings, followed by a small test battery recording of approximately 30 minutes that consists of a Mismatch negativity paradigm and a Selective attention paradigm. For details see below.

Quality of life

To broaden the scope of ECT treatment and possible positive effects of rivastigmine add-on, we will assess quality of life of the patients. Quality of life will be assessed using the Euro-QoL-5D-5L: This simple, reliable and widely used tool to assesses the quality of life of patients is included to not only get measures of cognitive functioning and depressive symptomatology but also to assess the intervention more comprehensively. It is administered in about 5 minutes.

Disability assessment

To assess the global level of disability, and specifically, if ECT and rivastigmine have positive effects on the experiences disability, we will use the WHODAS 2.0: World Health Organization Disability Assessment Schedule (WHODAS 2.0 12 item version). The WHODAS 2.0 12 item version is a short and validated assessment scale that measures the disability of/experienced by patients. The 12-item version takes about 5 minutes to complete.

Expectation of response

At each visit we will ask the patient to assess their own expectation of the likelihood that they will recover. The same question will be asked to the treating physician. The question will range from -5 (negative effect expected) to 5 (positive effect expected). This is to assess expectations on clinical outcomes and should not take longer than a minute.

PRAAT

Language production (PRAAT) will be assessed by an automatic analysis of spoken language. Patients will be asked to answer questions on neutral topics; their answers will be recorded using a head-worn microphone. Patients will be asked to talk for approximately five minutes, with a maximum of ten minutes. A set of open-ended questions will be used to elicit speech. If a patient does not wish to answer a particular question, it will be skipped. The speech recordings will be converted to writing using automatic speech recognition. The recordings will be automatically parsed and annotated using computer learning language systems

National adult reading test (NART, Dutch Version)

The NART is a quick reading test to determine a participants premorbid IQ. The NART is well validated and widely used in medical research. The protocol (yet to be published by the GEMRIC consortium) aiming to increase worldwide consensus in cognitive ECT research, also recommends this test. The NART will only be used at baseline, since it determines premorbid IQ and is believed to be robust to clinical change.

Cognitive Failures Questionnaire

The cognitive failures questionnaire (CFQ) measures self-reported impairments in perception, memory, and motor function. The questionnaire consists of 25 questions rated on a 5-point likert scale and takes about 5-10 minutes to complete. The total score reflects overall cognitive failures, whereas four subscales (identified using factor analysis) reflect failures in memory, distractibility, social blunders and names.

Subjective Assessment of Memory Impairment (SAMI)

The SAMI consists of two questions which are rated on a 10 and 5-point likert scale. The first question concerns the subjective feeling of memory point, and is rated from 0 no impairment, to 10 severe impairment. The second question concerns the impact of cognitive adverse events, rated from 1 no complaints, to 5 severe complaints (this will take up 1 minute).

Comprehensive assessment of symptoms and history (CASH)

The CASH was developed to measure sociodemographics, the psychiatric history of the patients, information about first-degree family, urbanity, immigration, and drug use and as screening tool for complaints other than psychotic illness. In the current study it will be used to assess and collect data pertaining to these subjects. Section 3 of this interview contains questions regarding alcohol and drug use, and will be used separately in the visits V1, V2 and V3.

Study description

Background summary

Electroconvulsive therapy (ECT) is the most potent psychiatric treatment, with an effect size of 1.5 for severe and refractory unipolar and bipolar depression. ECT convincingly outperforms pharmacotherapy such as tricyclic antidepressants and monoamine oxidase inhibitors and any form of psychotherapy. Despite its outstanding performance in reducing depressive symptoms up to the point of full remission, it is used only frugal. A recent Dutch study calculated that currently only 1.2% of chronic depressive patients are offered ECT, while 26% could actually benefit from this treatment. Unfortunately, the response to ECT is largely unpredictable, while cognitive side-effects occur frequently.
In a previous study, we found that multiple cognitive tests showed a significant decline immediately post-ECT, which resolved within 6 months after the last ECT session. Even though cognitive side-effects are mostly short-lasting, patients and doctors see this as a great drawback of ECT. If these disturbing side-effects could be prevented, more patients and psychiatrists would choose ECT as a treatment option for this severely ill group. This would lead to a more effective treatment and hence shorter duration of chronic severe depression and improvement in quality of life, while costs for health care and loss of productivity would decrease. A potential way of ameliorating side effects, could be to add a cholinesterase inhibitor to ECT treatment. Recent rodent studies show that the loss of cholinergic fibers specifically correlated to the cognitive side effects of rodents after electroconvulsive stimulation (ECS). We select rivastigmine (a cholinesterase inhibitor) as a potential candidate in counteracting cognitive side effects induced by cholinergic fiber loss due to ECT. Rivastigmine patches are very well tolerated and widely used for Alzheimer*s Disease.
Tailoring treatment to patients that are likely to respond while cognitive side-effects are unlikely to occur, would be another important

improvement of clinical care for patients with otherwise treatment-resistant depression. Currently, ECT treatment outcome is unpredictable. Factors that favor response include older age, psychotic depression, shorter duration of the depressive episode, rapid response (if patients respond before the 6th session, the chance of remission is higher) and smaller dentate gyrus volumes. However, these predictors are insufficiently accurate to make individual response profiles. Accurately classifying specifically non-responders will prevent application of ineffective treatment with potential iatrogenic damage, while more accurately predicted response will increase the applicability of ECT as treatment option. A potentially powerful way which is easy to implement in the clinic is prediction of ECT treatment response using EEG characteristics in addition to clinical information.

Study objective

This study has been transitioned to CTIS with ID 2024-518047-37-01 check the CTIS register for the current data.

The aim of our study is two folded: first, we aim to improve cognition after ECT, improving its acceptability and tolerability and hence increase its application. If ECT would be used for the calculated 26% of patients who have chronic severe depression, morbidity and mortality of this disorder would decrease steeply. Second, we aim to develop a prediction method based on clinical and EEG characteristics, to accurately predict who will respond to ECT. If it is possible to accurately predict ECT response (and non-response), it could be prevented that patients with a low chance of recovery receives ECT without response but with the associated risks.

Study design

Patients with a severe depressive episode indicated for ECT and treated as outpatient at or admitted to the University Medical Centre Utrecht (UMCU; or nearby center) or University Medical Centre Groningen (UMCG), between May 2021 and January 2025 will be asked to participate by the treating psychiatrist/nurse/psychologist.

Intervention

Rivastigmine add-on treatment during ECT treatment.
Patients will receive either placebo or rivastigmine, randomised in a 1:1 ratio. Rivastigmine will be added to the ECT course: in the first two weeks patients will receive a 4.5mg rivastigmine patch per day, and after the first weeks a 9.6mg catch will be given each day.
When ECT treatment stops, rivastigmine treatment will stop as well.

Study burden and risks

Rivastigmine is well tolerated and safe. It has been shown that rivastigmine administered as patches has a more favorable side effect profile than rivastigmine in oral capsule form [incidence of side effect are about three times fewer. Rivastigmine is effective for mild to moderate AD and PDD for several cognitive measures. The side effects associated to rivastigmine in patches are for the majority gastrointestinal (about 6-7%: vomiting, nausea, diarrhea), which is expected for cholinesterase inhibitors. Less frequent side effects for rivastigmine patches are headaches (3%) and dizziness (2%). The side effects were usually present during the titration phase (i.e. during the first weeks at 4.5 mg) and gradually disappear during maintenance phase. Urine incontinence is a rare but disturbing side effect. In addition, mild skin reactions may occur at the location of the patch. No serious adverse events that needed treatment are reported for rivastigmine in clinical trials.

No direct pharmacokinetic drug-drug interactions are observed for rivastigmine, including common drugs like digoxin, warfarin, diazepam, and fluoxetine. And no contraindications exist for rivastigmine use, except for an allergic reaction to rivastigmine (Summary of Product Characteristics). Note that patients receiving ECT are usually given succinylcholine for muscle relaxation. Rivastigmine may exaggerate the effects of succinylcholine leading to prolonged muscle relaxation. However, succinylcholine causes rapid and short muscle duration of muscle relaxation (~ 4-6 minutes) whereas the alternative to succinylcholine would be rocuronium which has a duration of action of 30-60 minutes (half-life of 66-80 minutes). So even if rivastigmine increases the time of muscle relaxation by 4-5 times, it will be on average shorter than the alternative rocuronium. However, we will carefully monitor the extent of (prolonged) muscle relaxation using the clinically validated Train of Four (TOF) assessment. In addition, we will administer the patches the evening before each ECT session, aiming for the Cmax of rivastigmine to be achieved during the night instead of during administration of succinylcholine.

In view of possible additive effects (possibly leading to bradycardia) no concomitant cholinomimetic drugs should be given next to rivastigmine. In addition, caution is warranted when administering rivastigmine with betablockers and torsades de pointes inducing drugs [such as antipsychotics like chlorpromazine (section 4.5 SPC rivastigmine, patch)].

Of note, one study investigating the addition of rivastigmine to haloperidol treatment in the management of delirium in critically ill patients was terminated early due to increased mortality in the rivastigmine group. The population of that study (critically ill patients admitted to the intensive care unit) is significantly different from the population of our study. Furthermore, the method of administration in the current study (transdermally) is different from that of the study by van Eijk et al., (2010; as a solution). Transdermal administration of rivastigmine leads to slower release and uptake of rivastigmine. Furthermore, in post-hoc analyses, the authors were unable to exclude the possibility that the increased mortality in the rivastigmine group

was due to chance. Given the fact that these patients were critically ill, which is not the case in the current study, and the absence of other reports on increased mortality with rivastigmine use, we do not expect that rivastigmine in the current study would pose a serious risk to the patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Ageover 18 years
- Clinical indication for ECT (as indicated by the treating physician/psychiatrist)
- Depressive disorder (as assessed by the treating psychiatrist)
- Dutch as first language

Exclusion criteria

- Currently using rivastigmine, galantamine, donezepil (all cholinesterase inhibitors for mild to moderate Alzheimer*s Disease).
- Pregnancy and/or lactation/breast feeding
- Suspicion of neurodegenerative disorders (as diagnosed earlier)
- Contraindications for ECT (recent myocardinfarct, recent cerebrovasculair accident, recent intracranial surgery, pheochromocytoma and instable angina pectoris)
- Contraindications for rivastigmine (bradycardia or atrioventricular (AV) conduction disorders (first degree AV-block excluded))
- Patients who have had an allergic reaction to rivastigmine
- Cognitive disorder not explained by the depressive episode
- If receiving outpatient ECT treatment, having no person available to apply the rivastigmine/non-active patch

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-09-2021
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rivastigmine

Generic name:	Rivastigmine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-03-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-07-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-518047-37-01
EudraCT	EUCTR2020-005633-33-NL
CCMO	NL76045.041.21