EMECLO: the Electroconvulsive therapy vs. MEdication in patients with CLOzapine-refractory symptoms trial

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Ethical review	Approved WMO
Status	Completed
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON53720

Source
ToetsingOnline

Brief title
EMECLO

Condition

- Schizophrenia and other psychotic disorders

Synonym
Clozapine resistent schizophrenia, therapy resistant psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Psychiatrie
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Aripiprazole, Clozapine, ECT, Schizophrenia

Outcome measures

Primary outcome

The main endpoints of this feasibility study are 1. The proportion of patients willing to be randomized in this study. To that end, we will record the total number of eligible patients asked to participate in the trial and the number of eligible patients willing to be randomized who actually are randomized. Then we will compute the proportion of those willing to participate. 2. The number of participants we are able to recruit in 8 months* time. 3. the dropout rate of the study.

Secondary outcome

In addition, 4. effect sizes of the outcome measures of the foreseen trial will also be assessed. The primary outcome of the foreseen trial is: difference between the two arms in QoL measured using the EQ5D (https://euroqol.org/) from baseline until 10 weeks after treatment inception. Secondary outcome measures include: differences in PANSS (Positive and Negative Syndrome Scale; positive and negative symptoms analysed separately as well as total symptoms) from baseline to 10 and to 16 weeks between both arms; differences in response (>=20% reduction of total or positive symptoms on the PANSS), clinical global impression-schizophrenia (CGI-S), recovery (Recovery Assessment Scale, RAS), depressive symptoms (Calgary depression scale for schizophrenia, CDS), all-cause discontinuation, number of (S)AEs and Cost effectiveness assessed through questionnaires (Medical Consumption Questionnaire and Productivity Cost

Questionnaire, iMCQ and iPCQ) from baseline to 10 and at 16 weeks.

Study description

Background summary

Clozapine (CLZ) is a last-resort antipsychotic agent used in the treatment of schizophrenia- spectrum disorders (SSD). Although benefits of CLZ have been demonstrated in a range of clinical situations [1-3] approximately 60% of patients considered treatment resistant do not fully respond to CLZ, i.e. are CLZ-refractory (CR), meaning they experience important residual psychiatric and physical symptoms on CLZ, hampering their social functioning and reducing quality of life (QoL) [4]. Although CR is common and has a substantial negative effect on the quality of life of the affected patients and their families, current guidelines do not offer clinicians clear advice on the best treatment in this situation. Increasing evidence suggests addition of electroconvulsive therapy (ECT) to clozapine is a safe and effective treatment in CR patients [5]. On the other hand, meta-analyses suggest that aripiprazole (ARI) addition to CLZ[6, 7] is a promising treatment strategy in CR patients. However, it is unknown how these treatment strategies compare to one another as head-to-head comparisons for add-on options to CLZ in CR patients are lacking. Such a comparison is relevant not only to assess potential efficacy and cost-effectiveness but also to establish possible differences in AEs burden between strategies as both ECT and medication augmentation with ARI have differential EA profiles. ECT is also relatively expensive and time-consuming compared with medication augmentation. Second, trials of treatment options for CR patients to date have focused on symptom reduction instead of a more comprehensive set of outcome measures including quality of life (QoL), AEs and recovery. Together, this emphasises the lack of evidence to assist clinical decision-making for CR patients. This knowledge gap is likely a consequence of inherent difficulties in designing and conducting a randomized trial in which (cost-) effectiveness and safety of treatments are compared in CR patients. The first factor explaining this currently unmet need is lack of knowledge about randomization willingness. Second, it is unknown how many participants can be included as well as what the attrition rate in such a trial will be. And third, since no studies have compared ECT with ARI, the magnitude of the effect sizes for the differences in outcomes between the two arms is unknown. Considering the challenges of performing a RCT in this specific, severely affected patient group, it is important to first study the feasibility of such a trial in a preparatory study in order to strategically optimize the eventual randomized trial.

Study objective

The main objective of this study is to investigate the feasibility of a larger single-blind, randomized trial focused on (cost) effectiveness and safety of ECT vs. aripiprazole addition in patients with schizophrenia spectrum disorders (SSD) insufficiently responsive to clozapine. The specific research questions addressed are: 1.How many of the patients eligible for inclusion are willing to be randomized? 2.How many patients will we be able to recruit?; and how many will we lose to follow-up at what stage of the trial? 3.What is the magnitude of the effect sizes in both arms that can be expected?

Study design

The current study is a multi-center preparatory, single-blind, randomized, head-to-head clinical feasibility study. Participants are randomized at 1:1 to i) addition of ECT; ii) addition of ARI. The outcome of this preparatory study will be used to design a foreseen large-scale single (rater)-blind, randomized trial focused on (cost) effectiveness and safety of ECT vs. aripiprazole addition to clozapine in patients with schizophrenia spectrum disorders (SSD) insufficiently responsive to clozapine. A superiority design was chosen given the increased costs and burden on patients involved with ECT relative to aripiprazole addition.

Intervention

Arm 1: ECT addition to clozapine. Bilateral ECT will be started twice weekly for 10 weeks and then in responders (i.e. those with either positive or total symptom reductions >= 20%) tapered to once weekly for an additional 6 weeks (total number of ECT sessions = 26). Non-responders at 10 weeks will discontinue ECT but will be followed up.
Arm 2: Addition to clozapine of aripiprazole (ARI) for 16 weeks (same duration of treatment as ECT).
All participants continue CLZ at the blood level they receive at study entry during the trial.

Study burden and risks

Participants could have a direct benefit as the studied interventions may lead to improvement of their symptoms and quality of life. The main risk is that of adverse effects (AEs) of either ECT or ARI, in which case patients and clinicians may decide (based on shared decision making) to lower the dose of ARI, or discontinue the treatment and switch to another agent, which is also in line with clinical practice. In the ECT arm, non-responders at 10 weeks will discontinue ECT but will be followed up. If participants do not respond (<20% response at week 16) with the treatment they are randomized to, they will be provided the oppertunity to cross-over to the other treatment. Should AEs arise, clinicians and patients may in the interest of shared decision-making decide to decrease ECT frequency or switch to right unilateral ECT.

Additionally, there will be a burden in time for patients undergoing ECT, as they will have to come to the clinic for several hours twice weekly during the course of this treatment. To limit participant burden related to the data collection, to reduce the chances of COVID-19 transmission and to facilitate inclusion, outcomes will be assessed through video calling as much as possible by a central, blinded rater. Each of the three visits participants will undergo take about one hour, for which they will be financially compensated. If non-responders participate in the cross-over, there will be two additional visits at week 26 and 32 (10 and 16 weeks after cross-over intervention), which will take about one hour each. The participants will be financially compensated for these visits. Participants can also give consent for a naturalistic follow-up a year after randomisation. This visit will also take about one hour and the participants will be financially compensated for the visit.
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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• He/she currently uses CLZ or discontinued CLZ and is willing to restart CLZ, treated in inpatient or outpatient settings with a diagnosis of schizophrenia, psychotic disorder not otherwise specified or schizoaffective disorder, according to the DSM5 criteria,
• He/she is CR, meaning they failed to achieve Andreasen remission criteria, while on CLZ either for a minimum period of 12 weeks at a concentration >= 350 Ug/L or lower with incomplete tolerance to CLZ.
• His/her age must be >= 18 years old
• He/she must be able to speak and read Dutch
• He/she must be mentally competent and have decisional capacity with regard to a decision to participate in the current study

Exclusion criteria

• prior treatment with ECT or ARI concomitantly with CLZ;
• known intolerance to ECT or ARI; and ARI or ECT-related contra-indications, i.e. kidney failure (GFR<30ml/min) and conditions predisposing to kidney failure (e.g. dehydration, infections and hypovolemic shock); recent CVA or intra cranial surgery; feochromocytome; current instable angina pectoris; disorders in the use of alcohol defined as > 2 reported consumptions daily and/or a gGT of over 60U/L and liver failure.
• pregnancy or nursing or being of child-bearing age without appropriate contraception.
• A history of Parkinson*s disease
• Admission to a psychiatric unit involuntarily in the context of a *crisis maatregel* or treatment with ECT or aripiprazole is provided as compulsory care in the context of a *zorgmachtiging* (as described in the care plan (*zorg en afstemmingsplan*) of the patient) or 'terbeschikkingstelling (TBS)'.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-05-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aripiprazole
Generic name:	Aripiprazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2022
Application type:	Amendment

Review commission: METC Amsterdam UMC

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
EudraCT	EUCTR2021-006333-19-NL
CCMO	NL79853.018.21