Clonidine Augmentation Treatment in Schizophrenia

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The primary aim is to investigate whether six weeks augmentation with clonidine of the antipsychotic treatment will reduce positive and negative symptomatology of treatment resistant schizophrenia patients. Important secondary goals of this project...

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

Summary

ID

NL-OMON44666

Source
ToetsingOnline

Brief title
CATS-Study

Condition

- Schizophrenia and other psychotic disorders

Synonym
Psychotic disorder, schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Clonidine, Noradrenaline, Psychosis, Resistant Schizophrenia

Outcome measures

Primary outcome

Change in " Positive and Negative Symptom Scale (PANSS)" total compared to baseline.

Secondary outcome

-General functioning (tested by "Global Assessment of Functioning", GAF)

-Cognitive functioning (tested by "Brief Assessment in Cognition", BACS and "The Cambridge Neuropsychological Test Automated Battery", CANTAB)

-IQ assessment (tested by vocabulary and block design subsets of the Wechsler Adult Intelligence Scale (WAIS) and the Trail Making Test A & B)

-Depressive symptoms (tested by "Calgary Depression Scale For Schizophrenia", CDSS)

-Safety data will be evaluated by comparing incidences (number and percentage of subjects with at least one occurrence) of key SEAs and SUSARs (e.g. hospitalizations)

-Psychophysiological parameters (tested by "Copenhagen Psychophysiological Test Battery", CPTB)

Study description

Background summary

Schizophrenia is a major debilitating mental disease with an incidence of approximately 1% in the general population worldwide. Currently available

antipsychotics are only effective in reducing positive symptoms, without restoring cognition or alleviating negative symptoms. Between one-fifth and one-third of patients have little, if any, benefit from them. Treatment of these patients remains a persistent public health problem, as treatment resistant patients are often highly symptomatic, have a severely reduced quality of life and need extensive periods of hospital care. Therapy-resistant Schizophrenia patients also require a disproportionately high amount of the total health costs for schizophrenia. Clonidine is a noradrenergic *2A agonist, usually prescribed in the treatment of hypertension, but also in the treatment of Tourette*s syndrome and in the treatment of children with ADHD. Results of a recent performed pilot study from our study group and literature point at a potentially positive effect of clonidine on certain aspects of schizophrenia.
In our pilot study we found that in schizophrenia patients very often disturbed parameters of basic information processing normalized when they were treated with only one administration of low dose (between 25 and 75 µg) of clonidine. In schizophrenia, there is a correlation between these parameters of basic information processing and cognitive functioning, symptom severity and daily functioning. Therefore we expect that a longer treatment period with clonidine will improve not only positive symptom severity, but also notoriously treatment resistant negative symptomatology. We also expect an improvement in cognitive functioning and daily functioning.

Study objective

The primary aim is to investigate whether six weeks augmentation with clonidine of the antipsychotic treatment will reduce positive and negative symptomatology of treatment resistant schizophrenia patients. Important secondary goals of this project are to determine whether this treatment will improve cognitive functioning and daily functioning in these treatment resistant schizophrenia patients. Also, parameters of basic information processing, measured with EEG will be assessed as a secondary outcome.

Study design

In a typical randomized clinical trial (RCT), a total of 50 patients with schizophrenia with no or only partial response to clozapine will be randomized over two arms: in one arm patients will receive an additional daily dose of clonidine (50 µg) to their current antipsychotic treatment, while in the second arm patients will receive placebo added to their medication. Both treatments will be sustained for 6 weeks. In addition, 25 healthy controls will be included matched on age and gender to evaluate the extent of the expected effects in the patients, as well as to assess the impact of test-effects, since these are notorious in particular for cognitive assessments e.g.: 2. We choose a 6 weeks period to balance between rate of drop out and yet still being able to detect improvements in quality of life: cognition, sensory filtering and mismatch negativity are such basic human qualities, that improving them even

for a period as short as 6 weeks will definitely have a statistically significant positive impact on the patient*s quality of life.
Following inclusion, baseline assessments will be made, which will be repeated after periods of 3 and 6 weeks. To avoid too many influences of test-effects, cognition will be assessed only at baseline and after 6 weeks. The healthy controls will be assessed at these same intervals, but will receive no treatment at all.

Intervention

The main investigational product used in this study is clonidine, which is approved for the treatment of several disorders including high blood pressure, migraine and withdrawal symptoms that occur after stopping the use of opiates.

-25 patiënts will receive 50 micrograms clonidine once a day for six weeks, added to their own antypsychotics which will preferably kept stable during threatment period.
-25 patiënts will receive placebotablets once a day for six weeks, identical looking to the clonidine tablets. Patiënts will continue their own antipsychotica and these will preferably kept stable.
-25 healty controls will not undergo any treatment.

Study burden and risks

During the study, no invasive methods will be used. The total burden and risks for the patients is based on the following factors:
1. Time investment: the complete study consists of 3 visits, with a total time of 20 hours. A more detailled schedule of all protocol procedures can be found in Table 1 of the protocol.
2. Side effects of clonidine. Considering that generally, side effects of clondine are mild and considering that the dosage administered in our study will be very low, no severe side effects can be expected.

Risks will be minimized through:
-elaborate in- and exclusion criteria
-implementation of appropriate, pro-active safety measures (e.g. strict monitoring of onset and course of specific side effects)
-Applying specific "stopping rules", which means that in case patients seem to develop specific side effects, they will be dropped out of the study, after which appropriate follow-up takes place as well as treatment if necessary.

A complete consideration of risks and burden on one hand and benefits on the other is prodded in section 13.2 "synthesis" of the structured risk analysis of the protocol

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. A DSM-IV-R diagnosis of: 295.x (schizophrenia), schizophreniform disorder, or schizoaffective disorder)
3. A total PANSS score of at least 55
4. Age 18-50 years.
5. Patients are treated with antipsychotic medication
6. Written informed consent
7. Female patients of childbearing potential need to utilize a proper method of contraception
8. (oral anticonceptives, vaginal ring, hormonal patch, intrauterine device, cervical cap, condom, contraceptive injection, diaphragm) in case of sexual intercourse during the study.
Ad. A priority will be given to patients who achieve no or only partial response to clozapine as defined by a total PANSS score of at least 80.;Inclusion criteria healthy controls:
-Age between 18-50 years

-Good Physical and Mental Health meeting criteria "never mentally ill", which will be evaluated with a medical history checklist;
-Age between 18 and 45 years;
-Written informed consent of the subject.

Exclusion criteria

1. Presence of any of the contra-indications of clonidine as reported in the Summary of Product Characteristics (SPC).
2. Supine systolic blood pressure (SSBP) < 85 mm HG
3. Pre-existent orthostatic hypotension with a drop of systolic blood pressure of > 20 mmHg or a drop of diastolic blood pressure of >10 mmHg.
4. Supine heart rate (SHR) < 50 beats/min
5. Severe brady-arhytmias such as sick-sinussyndroom, second or third degree AV-block.
6. Pregnancy or breast-feeding. A urine pregnancy test will be performed at screening.
7. The use of drugs that affect the (nor)adrenergic system such as beta-blockes and mirtazapine.;Exclusion criteria healthy controls:
-Current use of any medication prescribed medication exclusive oral anticonceptives;
-Any subject who has received any investigational medication within 30 days prior to the start of this study;
-History of neurologic illness; History of psychiatric illness in first-degree relatives, evaluated with DSM-IV criteria;
-History of alcohol and drug abuse;
-BMI below 18.5.

Study design

Design

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

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	21-02-2015
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clonidine
Generic name:	Clonidine hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-09-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-04-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	4716
EudraCT	EUCTR2014-003008-53-NL
CCMO	NL50050.041.14