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Memantine as an adjunctive therapy to ongoing clozapine treatment: a proof-of-concept study and follow-up study

Submission date
26/11/2014

Recruitment status
No longer recruiting

Registration date
12/12/2014

Overall study status
Completed

Last Edited
26/10/2016

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Schizophrenia is a long-term mental illness that results in a number of psychological symptoms including hallucinations, delusions, confusion, changes in behaviour, lack of emotion and feeling apathetic. The condition is often treated with a combination of antipsychotic drugs. Schizophrenia, however, can be difficult to treat. Clozapine is the most effective antipsychotic known, but it offers only a partial easing of symptoms in 70% of patients, and 4% of patients do not respond at all. This has a serious negative impact on the patients quality of life. The current strategy used for developing new psychotropic drugs (drugs that affect the functioning of the brain) is too expensive, too time consuming and often incorrect. We suggest an alternative strategy that is grounded in the principles of functional psychopharmacology. This means selecting a drug that targets key psychological functions due to its pharmacological characteristics (how it affects the brain), running a study to see if the treatment has potential (a proof-of-concept-study) and then going on to develop a larger follow-up study. Memantine is a drug that is used to treat patients with moderate to severe Alzheimer's disease. Based on the results of a small proof-of-concept study, taking memantine and clozapine in combination is expected to improve symptoms in patients with treatment-resistant schizophrenia. Memantine is a drug that improves the signalling (function) in certain molecules in the brain called NMDA receptors. These are believed to function at lower levels than usual in people with schizophrenia. These receptors are essential for receiving signals in the brain and are associated with sensory perception (hearing, seeing, tasting etc), learning and memory. The memantine /clozapine combination therapy increases the function of NMDA receptors which help to relieve the symptoms of schizophrenia. We want to see how well the therapy works when compared with a placebo and also test how safe it is to take and how well-tolerated it is by patients.

Who can participate?
Outpatients with clozapine-resistant schizophrenia aged between 18-60.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 receive memantine for 11 weeks. Those in group 2 are given a placebo. After a two week break, or washout stage,

participants in group 1 are given the placebo and participants in group 2 are given the memantine for a further 11 weeks. Prior to taking part, the participants are informed of the possibility of continuing to take memantine in combination with clozapine, if this combination therapy proves to have beneficial effects in an open 1-year follow-up study. Patients who do not experience any clinical benefit to taking memantine after a treatment duration of 12 weeks in the proof-of-concept study can also be included in the follow-up study, but do not receive any clozapine add-on therapy.

What are the possible benefits and risks of participating?
The combination of memantine and clozapine may help with cognitive and social functioning, and schizophrenia symptoms leading to an improvement of daily functioning and quality of life. Memantine may have a beneficial effect on depressive and obsessive-compulsive symptoms. There are some side effects associated with taking the drugs clozapine and memantine.

Where is the study run from?
Mental Health Service Organisation North Holland North, Community Mental Health Division (Netherlands)

When is the study starting and how long is it expected to run for?
August 2013 to September 2015

Who is funding the study?
Mental Health Service Organisation North Holland North, Community Mental Health Division (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2011-003466-33

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
NL34101.094.12

Study information

Scientific Title
Memantine Add-On Therapy to Clozapine

Acronym
MAOTC

Study objectives
Augmentation of clozapine with memantine targets altered glutamatergic neurotransmission in schizophrenia and showed beneficial effects on several symptom domains in a first proof-of-concept study. This is a second, larger and more elaborate study of adjunctive memantine to clozapine in treatment-resistant schizophrenia, inspired by the unique functional psychopharmacological characteristics and positive findings of the first proof-of-concept study.

More information can be found at:
http://www.ncbi.nlm.nih.gov/pubmed/25002292
http://www.ncbi.nlm.nih.gov/pubmed/25002291
http://www.ncbi.nlm.nih.gov/pubmed/25121994

On 02/10/2015 the overall trial end date was changed from 16/09/2015 to 02/10/2015.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Central Committee on Research Involving Human Subjects, 29/01/2013
2. Medical Research Ethics Committee (MREC) of Alkmaar Medical Center, 17/05/2013

Study design
Proof-of-concept double-blind randomized placebo-controlled crossover trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Community

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Refractory schizophrenia with a non-satisfactory response to clozapine after a treatment duration of at least six months

Interventions
Proof-of-concept study
The proof-of-concept trial consists of two cross-over, 12-week treatment phases and a placebo wash-out period of two weeks in the 13th and 14th week to avoid carry-over effects. Subjects are randomly assigned to receive either an identical number of identical looking memantine or placebo tablets. During the first treatment phase subjects receive either placebo or memantine once daily, starting with 10 mg during the first week, built up in the second week to 20 mg during eleven weeks as add-on therapy to ongoing clozapine treatment. After cross-over in the second treatment phase (1 week titration and 11 weeks treatment) the group treated with placebo switches to memantine and vice versa.

Anticipated start date: 01/08/2013 and actual start date: 05/08/2013
Recruitment start date: 05/08/2013
Recruitment end date: 17/12/2013
Anticipated date of last follow-up: 01/08/2014 and actual date of last follow-up: 05/08/2014
Actual date of closure to data entry: 05/08/2014 and date trial data considered complete: 10/09/2014

Follow-up study
In the follow-up study, patients who have experienced beneficial effect of memantine will receive memantine add-on therapy to clozapine. Patients who have not experienced clinical improvement after 12 weeks of memantine addition in the proof-of-concept study will not receive any other clozapine add-on therapy.

Anticipated and actual start date: 07/08/2014
Recruitment start date: 07/08/2014
Recruitment end date: 22/08/2014
Anticipated date of last follow-up: 11/09/2015
Planned date of closure to data entry: 16/09/2015 and date trial data considered complete: 02/10/2015

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Memantine

Primary outcome measure

1. Cognitive functioning, assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized, non-linguistic cognitive testing battery (Levaux et al., 2007), consisting of eight tests:
1.1. Motor screening (MOT) for induction
1.2. Rapid Visual Information Processing (RVP) and Reaction Time
1.3. Simple and 5 Choice (RTI) for attention
1.4. Verbal Recognition Memory (VRM)-immediate (free recall) and Verbal Recognition Memory (VRM)-delayed (recognition) for verbal memory
1.5. Paired Associates Learning (PAL) for visual memory
1.6. One Touch Stockings of Cambridge (OTS) and Spatial Working Memory (SWM) for executive function.

Other primary outcomes are:
2. Severity of psychopathology (Clinical Global Impression Severity Scale [CGI-S])
3. Positive, negative and overall symptoms of schizophrenia (Positive and Negative Syndrome Scale [PANSS])

In the proof-of-concept study assessments take place at baseline, 12 weeks (phase 1), 14 weeks (after wash-out), 26 weeks (phase 2) or at withdrawal of study. In the follow-up study assessments take place at baseline, 26 weeks, 52 weeks or at withdrawal of study.

Secondary outcome measures
1. Depressive symptoms (Calgary Depression Scale for Schizophrenia [CDSS])
2. Social cognition (Reading the Mind in the Eyes test [RME] for theory of mind and Emotion Recognition Task [ERT] of the CANTAB for facial emotion recognition)
3. Obsessive-compulsive symptoms (Yale-Brown Obsessive-Compulsive Scale [Y-BOCS])
4. Psychosocial symptoms (Health of the National Outcome Scales [HoNOS]
5. Quality of life (Manchester Short Assessment of Quality of Life [MANSA])
6. Side effects (Liverpool University Neuroleptic Side-Effect Rating Scale [LUNSERS] and a list of possible side effects of memantine which are not mentioned in the LUNSERS (thrombosis, dyspnea and mycosis) specifically noted in Likert ratings)
7. Safety measures (blood pressure, waist circumference and laboratory tests of blood glucose, lipids, liverenzymes, renal function, white blood cell count and differentiation, plasma clozapine level)
8. Drop-out rate

In the proof-of-concept study assessments take place at baseline, 12 weeks (phase 1), 14 weeks (after wash-out), 26 weeks (phase 2) or at withdrawal of study. In the follow-up study assessments take place at baseline, 26 weeks, 52 weeks or at withdrawal of study.

Overall study start date
05/08/2013

Completion date
02/10/2015

Eligibility

Key inclusion criteria
The inclusion criteria for the proof-of-concept study include:
1. Outpatients (including sheltered housing) and patients living in long-stay wards

2. Both sexes
3. Age 18 to 60
4. Meeting DSM-IV criteria for schizophrenia, based on the definitions in the Mini International Neuropsychiatric Interview Plus (MINI-Plus) with persistent residual psychopathology
5. Failing to achieve the remission criteria (remission is defined as simultaneous ratings of mild or less (≤ 3 points) on eight of the PANSS items evaluating the core symptoms of schizophrenia (P1 delusions, G9 unusual thought content, P3 hallucinatory behaviour, P2 conceptual disorganisation, G5 mannerisms and posturing, N1 blunted affect, N4 passive or apathetic social withdrawal, N6 lack of spontaneity and flow of conversation)
6. Before the start of the study clozapine plasma concentration has been at least 350 ng/ml for 12 weeks or has not reached 350 ng/ml due to intolerability
7. Able to understand the study information and procedures and give informed consent.

The inclusion criteria for the follow-up study include:
1. Completer of the proof-of-concept study.
2. Memantine is only administered to patients who have experienced clinical improvement after 12 weeks of memantine addition in the proof-of-concept study.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
The end of trial is reached when at least 42 of 52 included patients have received randomly the verum in maximum dosage for 11 weeks and placebo for 12 weeks

Key exclusion criteria
1. Patients admitted at acute treatment wards
2. Pregnancy
3. Lactating women
4. Female subjects without adequate contraception
5. Known hypersensitivity to memantine
6. Co-medication with glutamate modulators
7. Lactose intolerance
8. Uncontrolled epilepsy
9. Myocardial infarction
10. Uncontrolled hypertension
11. Renal insufficiency
12. Severe liver failure
13. Moderate or severe Alzheimer’s disease
14. Extremely ill patients (Global Assessment of Functioning [GAF] ≤ 20), who are not reliably able to give their informed consent

Date of first enrolment
05/08/2013

Date of final enrolment
22/08/2014

Locations

Countries of recruitment
Netherlands

Study participating centre
Mental Health Services North Holland North, Community Mental Health Division
Oude Hoeverweg 10
Alkmaar
1816 BT

Sponsor information

Organisation
Mental Health Service Organisation North Holland North, Community Mental Health Division

Sponsor details
Oude Hoeverweg 10
Alkmaar
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1816 BT

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00b3xjw51

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Mental Health Service Organisation North Holland North, Community Mental Health Division (Netherlands)

Results and Publications

Publication and dissemination plan
We intend to submit an article on the proof-of-concept study shortly, probably in March 2015. An article on the follow-up study will follow probably a year later. The study was a prospective study, conducted in accordance to the protocol described in the EU Clinical Trials Register, which is also online.

Intention to publish date
31/03/2016

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2016		Yes	No
Results article	results	01/01/2017		Yes	No