Memantine Add-On Therapy to Clozapine

Published: 29-01-2013
Last updated: 26-04-2024

This proposal entails a proof-of-concept study into the neuropsychological effects of memantine augmentation in a random cross-over comparison to placebo, as add-on treatment to ongoing clozapine in severely mentally ill (SMI) patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39302

Source
ToetsingOnline

Brief title
MAOTC

Condition

- Other condition
- Schizophrenia and other psychotic disorders

Synonym
clozapine-refractory schizophrenia - treatment resistant schizophrenia

Health condition

in het bijzonder therapieresistente schizofrenie (langer dan 6 maanden ingesteld op clozapine)

Research involving
Human

Sponsors and support

Primary sponsor: GGZ NHN
Source(s) of monetary or material Support: GGZ NHN financiert alle kosten;die verbonden zijn aan het onderzoek. De memantine- en placebotabletten zullen gratis worden geleverd door de farmaceut Lundbeck.,Lundbeck

Intervention

Keyword: Clozapine, Glutamate, Memantine, Schizophrenia

Outcome measures

Primary outcome

a. Cognitive functioning will be assessed by the Cambridge Neuropsychological

Test Automated Battery (CANTAB), an outstandingly sensitive and extensively

validated cognitive testing battery. The tests are computerized, non-linguistic

and culturally blind, consisting of 9 tests:

1. Motor screening (MOT) (3 minutes);

2. Verbal Recognition Memory (VRM)-immediate (20 minutes);

3. Rapid Visual Information Processing (RVP) (7 minutes);

4. Intra/ Extradimensional Set Shifting (IED) (7 minutes);

5. Reaction Time: Simple and 5 Choice (RTI) (5 minutes);

6. Verbal Recognition Memory (VRM)-delayed;

7. One Touch Stockings of Cambridge (OTS) (10 minutes);

8. Paired Associates Learning (PAL) (7 minutes);

9. Spatial Working Memory (SWM) (8 minutes).

b. Severity of psychopathology and treatment response:

1. Clinical Global Impression Severity Scale (CGI-S), a 7-point scale that

requires the clinician to rate the severity of the patient's psychiatric illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy, 1976).

2. Subscale for positive symptoms of the Positive And Negative Syndrome Scale, based on a semi-structured interview (SCI-PANSS). The PANSS is a validated measure and it is the most widely used scale to assess the symptoms of schizophrenia. This 30-item rating scale is designed to measure severity of psychopathology, reporting five components: positive, negative, depression, agitation-excitement and disorganisation (Kay et al 1987). The administration time of the SCI-PANSS is approximately 30 to 40 minutes.

3. Subscale for negative symptoms of the Positive And Negative Syndrome Scale, (SCI-PANSS).

Secondary outcome

a. Severity of depressive symptoms:

1. Calgary Depression Scale for Schizophrenia (CDSS); a semi-structured goal directed interview with an administration time of approximately 10 to 15 minutes, especially designed to distinguish depressive symptoms from negative symptoms and extrapiramidal symptoms in patients with schizophrenia (Addington et al, 1990).

b. Social cognition will be assessed by 2 computerized tests:

1. Reading the Mind in the Eyes test (theory of mind) (10 minutes);

2. Emotion Recognition Task of the CANTAB (facial emotion recognition) (15

minutes).

c. Obsessive-compulsive symptoms:

1. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), based on information collected in a semi-structured interview of 10 items with an administration time of approximately 10 to 15 minutes (Goodman et al, 1989).

d. Psychosocial functioning:

1. Health of the National Outcome Scales (HoNOS), the most widely used routine clinical outcome measure used by English mental health services. The test is simple, reliable and valid to measure the health and social functioning of people with severe mental illness (Wing et al, 1999). The HoNOS consists of 12 items with 4 subscales: behavioral problems, impairments, symptoms and sociale problems. All items are assessed on a 5-point Likert scale. The administration time amounts to approximately 5 to 15 minutes.

e. Quality of life:

1. Manchester Short Assessment of Quality of Life (MANSA) a reliable, valid questionnaire for registration of subjective quality of life (Priebe et al, 1999). The MANSA consists of 16 items. The administration time amounts to approximately 5 minutes.

f. Safety measures:

1. Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) is a

51-item self-rating scale for measuring neuroleptic induced side-effects (Day et al., 1995). The administration time amounts to approximately 15 minutes.

2. Possible side effects of memantine, which are not mentioned in the LUNSERS (thrombosis, dyspnea and mycosis) are specifically noted in Likert ratings.

3. Laboratory tests (fasting plasma glucose, triglycerides, LDL, HDL and total cholesterol, liverenzymes, renal function, white blood cell count and differentiation, because of the risk of clozapine-induced agranulocytosis and plasma clozapine level) (10 minutes).

4. Blood pressure and waist circumference (10 minutes).

g. Drop-out rate.

Study description

Background summary

The current (DSM) psychiatric diagnosis driven strategy for developing new indications for psychotropic drugs is too expensive, too time consuming and often invalid. We suggest an alternative, more efficient strategy that is grounded in the principles of functional psychopharmacology. This strategy entails: a) the selection of drugs that specifically target key psychological functions due to their pharmacological characteristics, b) conduction of proof-of-concept-studies for their introduction. Memantine is a NMDA receptor antagonist, which, in combination with clozapine, is expected to improve cognitive and social dysfunctions as well as negative and positive symptoms in patients with treatment resistant schizophrenia. To demonstrate the utility of the proposed strategy, the clinical value, tolerability, and safety of the NMDA antagonist memantine will be evaluated versus placebo in combination with ongoing clozapine treatment in patients with severe mental illness (SMI).

Lucena et al. (2009) treated 21 outpatients with refractory schizophrenia with prevailing negative symptoms with either 20 mg memantine daily or placebo in addition to clozapine for 12 weeks. A remarkable improvement was found on the total BPRS score (effect size = - 2,75), its subscales of positive symptoms

(effect size = - 1.38), negative symptoms (effect size = - 3.33), the CGI score (effect size = -1.56) and the MMSE (Mini-Mental State Exam) score (effect size = 1.32). No significant changes in weight nor extrapyramidal symptoms were observed using the Simpson-Angus Scale (SAS). In a six-week open-label study by Krivoy et al. (2008) seven inpatients with refractory schizophrenia received memantine with weekly increasing dosage (5, 10, 15, 20 mg) in addition to ongoing antipsychotic treatment. All patients received first generation antipsychotics in a long acting formulation and one patient received a combination of zuclopentixol and clozapine. A significant improvement was found of the PANSS score with the most prominent beneficial effect on negative signs, leading to a total decrease of 21% between endpoint and entry scores. Also improvements of the positive subscale of the PANSS score (15.6%) and the BPRS (Brief Psychiatric Rating Scale) (18%) were reflected in clinical global impression of change (CGI) (19%). Cognitive status showed no improvement, but the lack of effect on cognitive functioning could be related to the relatively short duration of memantine intervention (three weeks at maximal dosage). A placebo-controlled study for 8 weeks by Lieberman et al. of 136 patients with persistent residual psychopathology of schizophrenia showed no efficacy of memantine as an adjunctive treatment to other atypical antipsychotics than clozapine. Possibly when clozapine and memantine are combined, a special glutamatergic environment is created in which clinical improvement is sustained.

Study objective

This proposal entails a proof-of-concept study into the neuropsychological effects of memantine augmentation in a random cross-over comparison to placebo, as add-on treatment to ongoing clozapine in severely mentally ill (SMI) patients with refractory schizophrenia. A secondary aim is to demonstrate clinical and biological effects and to assess its tolerability. The neuropsychological variables are selected to be predictive of the beneficial effects concerning the severity of the clinical, cognitive, and social handicaps of SMI patients. Negative symptoms of schizophrenia are known to predict worse social outcome. In addition to negative symptoms, residual positive symptoms, debilitating cognitive disturbances, impaired social cognition, and depressive symptoms contribute to functional impairment and reduced quality of life. These are considered to reflect the need for care in daily living and the quality of life of these more severily ill patients. Treatment of poor-outcome patients with clozapine-resistant schizophrenia is costly and challenging. If this proof-of-concept study on addition of the NMDA antagonist memantine shows relevant clinical improvement in patients with clozapine-refractory schizophrenia, clinical investigation should be the follow-up for this augmentation strategy. The full project therefore consists of a proof-of-concept study, followed by a monitored release project as a prerequisite for financial reembursement. This proposal is limited to the first part of this project.

The project has two aims: a) in general, following functional psychopharmacological principles, to develop a procedure for identifying drugs with psychopharmacological properties that specifically target specific psychopathological dysfunctions, and b) to demonstrate the utility of this research approach in the treatment of refractory severely mentally ill patients.

Primary research questions:
1. Is memantine efficacious as an adjunctive treatment to clozapine in patients with refractory schizophrenia to improve cognitive impairment?
2. Does memantine in combination with clozapine diminish the severity of psychopathology, positive and negative symptoms?

Secondary research questions:
1. Does memantine have a beneficial effect on depressive symptoms?
2. Does memantine add-on therapy to clozapine have a beneficial effect on social cognition?
3. Does memantine improve obsessive-compulsive symptoms?
4. Are there differences in efficacy and tolerability of clozapine treatment combined with memantine compared to clozapine treatment in combination with placebo in other areas of clinical outcome: psychosocial functioning, quality of life and dropout rate?

Study design

Study design:
A proof-of-concept cross-over, placebo-controlled cross-over study examining the pharmacological efficacy of memantine versus placebo as add-on therapy to ongoing clozapine treatment in patients with refractory schizophrenia.

Study setting:
Outpatients, age 18 to 60, both male and female, meeting DSM-IV criteria for schizophrenia, based on the definitions in the Mini International Neuropsychiatric Interview Plus (MINI-Plus) with persistent residual psychopathology, failing to achieve the remission criteria, after adequate treatment with clozapine for at least 6 months. 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. Remission is defined as simultaneous ratings of mild or less (<= 3 points) on 8 of the PANSS items evaluating the core symptoms of schizophrenia (simultaneous ratings of mild or less (<= 3 points) on 8 of the PANSS items evaluating the core symptoms of schizophrenia) and a nonsatisfactory response to clozapine (duration of clozapine treatment at least six months). Patients are recruited from in mental health facilities of North Holland North.

Study duration:
This study will consist of two double-blind, randomized cross-over phases of 11

weeks testing the effects of the maximal daily dosage of 20 mg memantine (after a titration phase of 1 week). The length of the washout period will be 2 weeks. The total study duration is 26 weeks.

Sample size proof-of-concept study:
Based on the study of Lucena et al. (Effect size = 0.55, α = 0.05, Power = 0.80) the sample size for a non-cross-over randomized controlled trial would amount to 84 patients.

t tests - Means: Difference between two independent means (two groups)
Analysis: A priori: Compute required sample size
Input: Tail(s) = One
Effect size d = 0.8
α err prob = 0.05
Power (1-β err prob) = 0.80
Allocation ratio N2/N1 = 1
Output: Noncentrality parameter δ = 2.5204166
Critical t = 1.6636492
Df = 82
Sample size group 1 = 42
Sample size group 2 = 42
Total sample size = 84
Actual power = 0.8036357

In order to perform a more accurate assessment of efficacy and safety of memantine addition to clozapine, this proof-of-concept study is a placebo controlled cross-over trial, in which each patient serves as his or her own control. Due to the cross-over study design a relatively small number of participants (half of patients calculated above) is required for this study to have enough power. Therefore at least 42 patients are needed to complete the study. Cross-over effects are negligible with a wash-out phase of 2 weeks.

Because of drop-out (estimated at 20%), 52 patients will be included.
Cross-over effects are negligible with a wash-out phase of 2 weeks.

Research/ treatment procedures:
1. Session in which the researcher provides information;
2. Session in which informed consent is obtained;
3. Baseline assessments for all patients;
4. Randomization and dose titration for 1 week according to protocol: random allocation to either verum or placebo treatment for 11 weeks. The dosage memantine starts with 10 mg daily and is increased with 10 mg daily after 1 week. In the second week patients receive either 20 mg (2 Ebixa®, 10 mg tablets), or 2 matching placebo tablets;
5. Phase 1 treatment: 11 weeks of treatment with combination of clozapine and memantine, or clozapine and placebo;
6. Single blind placebo wash-out period for 2 weeks: 1 placebo tablet daily;

7. Phase 2: patients treated with memantine switch to placebo and vice versa for 12 weeks (dose titration for again 1 week, followed by treatment in the maximal dosage of 20 mg memantine for 11 weeks);
8. Assessment at baseline, 12 weeks (phase 1), 14 weeks (after wash-out), 26 weeks (phase 2) or at withdrawal of study.

Time schedule of outcome assessment:
Assessment will take place at baseline, 12 weeks (phase 1), 14 weeks (after wash-out), 26 weeks (phase 2) or at withdrawal of study. All assessments will take place on one day, starting with a venipuncture (measurements a metabolic screening, plasma clozapine level), measurements of blood pressure and waist circumference, followed by the the PANSS, CANTAB, the tests for social cognition and other questionnaires.

Use of co-intervention:
To enhance generalizability to the reference population and the feasibility of the study, concomitant medications are allowed, but doses per day need to be documented throughout the study and all medication should remain as stable as possible. In case of concomitant medication changes (except for benzodiazepines; maximal dosage lorazepam 2,5 mg three times daily or its equivalent is allowed), we will end the double blind study for this patient, but will continue to follow the patient for further analysis. To monitor for potential confounders, co-medication and psychotherapeutic intervention will be assessed at baseline and at outcome assessments. Changes in lifestyle should be avoided. Use of substances such as nicotine, which interacts with clozapine, but also drugs and alcohol should not change during the course of the study.

Description and justification of route of administration and dosage:
In order to allow for good generalizability, the dose range is chosen according to clinical practice in patients with Alzheimer*s disease and the result of a recent trial (Lucena et al, 2009). Clozapine dosage is at the discretion of the treating physician, but will remain as constant as possible. Distribution will take place by tablets of 10 mg, containing either placebo or memantine. To maintain blind treatment assignment, bottles will also have identical appearance.

Intervention

Clozapine combined with ebixa (memantine) starting with 10 mg during the first week, built up after one week to 20 mg daily.

Study burden and risks

Burden:
Patients will be randomly allocated to addition of memantine or placebo to their ongoing treatment with clozapine (duration of clozapine treatment at

least six months). One session is needed to inform the patient on the study design and procedure. After the information session the patient has to give informed consent. After 2 weeks, 13 weeks and 26 weeks two sessions are needed to assess outcome data, possibly two extra sessions at drop-out. Before treatment initiation plasma clozapine level (12 +/- 0,5 hours after ingestion) will be measured. This measurement will be repeated after 13 weeks and 26 weeks. No additional venipuncture will be necessary since the investigational venipunctures will be combined with the regular venipunctures for regular controls of white blood cell count (WBC). At these three points of measurements a metabolic screening will be assessed (glucose sober in plasm, triglycerides, LDL, HDL and total cholesterol, including blood pressure and waist circumference).

Risk:
There is a risk on adverse effects related to the treatment with clozapine. This is no special risk related to the trial since the patient was treated with clozapine for at least 6 months prior to the start of the trial. Special risks of the trial are related to memantine, which is licensed for treatment of moderate and severe Alzheimer*s disease with a favorable safety and tolerability profile. The DCH GCP guidelines report no cause for concern, which can be considered as giving some reassurance, since memantine is on the market for nearly twenty years in Europe. No major differences have been reported in the frequency of SAEs between memantine and placebo. The majority of SAEs were assessed as unrelated to study medication. The safety and tolerability of memantine in combination with clozapine in patients with schizophrenia is widely unknown, although the trial of Lucena et al. did not show any differences in adverse events or changes in extrapyramidal symptoms between addition of placebo or memantine to clozapine (Lucena et al., 2009). In the study of Lieberman et al. addition of memantine was associated with a higher incidence of serious adverse events compared to placebo (8.7 versus 6.0%). Discontinuations of treatment because of adverse events were higher in the memantine group than in the placebo group (11.6 versus 3.0%). The most frequent adverse events in the memantine group were headache, insomnia, constipation, fatigue and dizziness (Lieberman et al, 2009). Careful clinical procedures will be performed to detect adverse events with weekly Likert scales and respond to them as needed. White blood cell counts will be monitored in all patients according to official regulations to detect clozapine-induced agranulocytosis. The dosage memantine will be increased during three weeks to the maximal, usual dosage of 20 mg daily. This dosage is also administered in Alzheimer's disease and other studies into the efficacy and tolerability of memantine for other indications than Alzheimer's disease. Clozapine dosage is at the discretion of the treating physician, but will remain as much unaltered as possible. Concomitant medications are allowed, but doses per day need to be documented throughout the study and all medication will remain as stable as possible. Although no pharmacokinetic interaction is known between clozapine and memantine, plasma clozapine level (12 +/- 0,5 hours after ingestion) will be measured at three points of measurements.

Benefits: The combination of memantine and clozapine may be associated with favourable effects on cognitive and social functioning, positive and negative symptoms, reflected in improvement of daily functioning and quality of life in patients with refractory schizophrenia. Possibly memantine has a beneficial effect on depressive and obsessive-compulsive symptoms.

Group relatedness: The study specifically targets patients with refractory schizophrenia, treated with clozapine, because the combination of clozapine and memantine is considered to create a specific glutamatergic environment, in which neurotransmission is improved and clinical improvement is sustained.

Contacts

Public
GGZ NHN

Rhijnvis Feithlaan 150C
Alkmaar 1813 KV
NL
Scientific
GGZ NHN

Rhijnvis Feithlaan 150C
Alkmaar 1813 KV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible for the study are outpatients, both sexes, age 18 to 60, meeting DSM-IV criteria for schizophrenia, based on the definitions in the Mini International Neuropsychiatric Interview Plus (MINI-Plus) with persistent residual psychopathology, failing to achieve the remission criteria, after adequate treatment with clozapine for at least 6 months. 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. Remission defined as simultaneous ratings of mild or less (<= 3 points) on 8 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) (Os van and Kahn, 2007). Patients should be able to understand the study information and procedures and give informed consent. All participants fulfilling the inclusion and not fulfilling the exclusion criteria may, after a detailed description by a doctor and the written declaration of informed consent on an according form, participate in the study.

Exclusion criteria

- Pregnancy.
- Lactating women.
- Female subjects without adequate contraception.
- Known hypersensitivity to memantine or ingredients used in this tablet.
- Uncontrolled epilepsy.
- Recent myocardial infarction.
- Uncontrolled hypertension.
- Renal insufficiency (GFR less than 30 ml/min).
- Severe liver failure (ASAT 175 U/l and/or ALAT 225 U/l in men and 175 U/l in women).
- Lactose intolerance.
- Co-medication with NMDA-antagonists such as amantadine, ketamine, dextromethorphan.
-Co-medication with glutamate antagonists such as lamotrigine and topiramate.
- Extremely ill patients (Global Assessment of Functioning [GAF] <= 20), who are not reliably able to give their informed consent.
- Moderate or severe Alzheimer*s disease.

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-08-2013
Enrollment:	52
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clozaril
Generic name:	Clozapine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ebixa
Generic name:	memantine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-01-2013
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO

Date:	17-05-2013
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2011-003466-33-NL
CCMO	NL34101.094.12