Glutamatergic medication in the treatment of Obsessive Compulsive Disorder (OCD) and Autism Spectrum Disorder (ASD)

Published: 21-12-2015
Last updated: 16-04-2024

The Primary objective is: 1) To investigate clinical effectiveness of the glutamatergic compound memantine in paediatric patients with: - Obessive-Compulsive Disorder (OCD) GOAT-1 - Autism Spectrum Disorder (ASD) GOAT-2 with respect to symptoms of...

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

Summary

ID

NL-OMON41943

Source
ToetsingOnline

Brief title
GOAT studies in TACTICS

Condition

- Other condition
- Communication disorders and disturbances

Synonym
Autism Spectrum Disorder and Obsessive Compulsive Disorder

Health condition

Obsessief Compulsieve Stoornis

Research involving
Human

Sponsors and support

Primary sponsor: Radboudumc, Donders Institute of Brain, Cognition and Behavior
Source(s) of monetary or material Support: EU FP7 (TACTICS subsidie)

Intervention

Keyword: Autism Spectrum Disorder, glutamatergic medication, Obsessive Compulsive Disorder, pilot study

Outcome measures

Primary outcome

Primary endpoints are measures of

* Baseline-to-endpoint change in symptoms/scale scores of compulsivity

(CY-BOCS Total score),

* adverse event rates and profile (spontaneous reporting, structured (short) AE

scale, laboratory measures).

Secondary outcome

Genotypes of single common and rare variants in candidate genes, and also

combined genetic variants in whole genes or neurotransmitter systems / gene

pathways;

Further lab assessments of various proteins in blood plasma.

Study description

Background summary

Compulsivity is a cross-disorder trait underlying phenotypically distinct psychiatric disorders that emerge in (early) childhood (ASD, OCD), or adolescence (addiction to substance use). Compulsivity is defined as the

repetitive, irresistible urge to perform a behaviour, the experience of loss of voluntary control over this intense urge, the diminished ability to delay or inhibit thoughts or behaviours, and the tendency to perform repetitive acts in a habitual or stereotyped manner (Chamberlain et al. 2006).
In this study the focus will be on compulsive behaviours across the different clinical phenotypes and the developmental links between compulsivity and impulsivity.

Obsessive Compulsive Disorders (OCD) are characterized by repetitive thoughts, impulses or images (obsessions) and repetitive behaviours or mental acts (compulsions). Autism Spectrum Disorders (ASD) are characterized by deficits in (i) reciprocal social interaction and (ii) communication, and by (iii) restricted, repetitive and stereotyped patterns of behaviour, interests and activities.

Compulsivity and the closely associated impulsivity trait are characterized by behavioural disinhibition maintained by maladaptive fronto-striatal circuits (Fineberg et al. 2010). Compulsivity has also been considered an overarching concept that includes both failure to resist an impulse or an urge (impulsivity), maladaptive habitual behaviours (addiction), repetitive motor behaviours, rituatlistic and stereotyped behaviours, and feelings of loss of control (ECNP, 2010).

Glutamatergic projections to and from frontal subregions to the striatum play a key role in the regulation of various compulsive behaviours in humans including: 1) a maladaptive habitual pattern (addiction), 2) repetitive motor behaviours (stereotypy in ASD) and 3) the feeling of loss of control (OCD). Glutamatergic imbalance in fronto-striatal regions has been observed, e.g., in childhood OCD (MacMaster et al. 2008).
This suggests that impaired functioning of both frontal and striatal areas may be due to a common underlying pathophysiology, such as dysregulation of glutamatergic mechanisms and glutamatergic genes.

Preclinical animal models of compulsivity support glutamatergic interventions, e.g., excessive stimulation of the orbito-frontal cortex and the anterior cingulate may result in the generation of excessive, erroneous glutamatergic signals to the basal ganglia, leading to compulsive behaviour.
Ongoing rodent studies in the TACTICS project will add to pre-existing knowledge by, e.g., providing proof-of-concept predictive data for glutamatergic medication strategies in both male and female models, with high relevance for the exploratory clinical studies in paediatric populations with OCD and ASD outlined in this study protocol.

Study objective

The Primary objective is:

1) To investigate clinical effectiveness of the glutamatergic compound memantine in paediatric patients with:

- Obessive-Compulsive Disorder (OCD) GOAT-1
- Autism Spectrum Disorder (ASD) GOAT-2

with respect to symptoms of
- *compulsivity* (assessed as CY-BOCs Total score)

Secondary objectives are:

(1) To explore the effects of glutamategic interventions at the level of the structure, function and biochemistry of the fronto-striatal circuits (MRI, MRS) (in subgroups (disorders, age range, meeting inclusion/exclusion criteria of the COMPULS study protocol from the TACTICS project).
(2) To collect: blood for genetic analyses and biomarkers.
(3) To explore: additional clinical outcomes, disorder-specific (e.g., core symptoms, response rates, social functioning).

Study design

This/these 15 week study(ies) has/have a
- Add-on, randomized, double-blind, placebo-controlled design of
- treatment with a glutamatergic compound (memantine),
- including an up-titration phase (forced flexible dose design),
- in paediatric patients with OCD, ASD.

Psychiatric and behavioural data will be collected, including measures of

(a) rigid and compulsive patterns of behaviour that are appropriate for these disorders,
(b) MRI and MRS data will be collected in subgroups (age range, disorders meeting inclusion/exclusion criteria of the COMPULS study protocol from the TACTICS project, cf. Annex).
(c) Blood will be collected for genetic analyses and for biomarkers.

Intervention

This study involves a comparison of an active drug (memantine) with matching placebo. During Study Period II, medication will be initiated and modified according to the weight group of the patient at Baseline (Visit 3). Dosing may then be increased (or decreased) by 5 mg/d increments, respectively, at specified visits/dates according to the weight of the subject. Stepwise

up-titration is recommended to the target dose or the highest tolerable dose by week 4, accordingly. Dosing should remain stable during the last 4 weeks of Study Period II, unless a dose reduction is necessary for safety or tolerability reasons.

Study burden and risks

The proposed study includes invasive measures, namely the collection of blood samples, and MRI sessions, both at different time points. To answer our main questions about the effect of glutamatergic interventions on the severity of clinical symptoms of compulsivity and on the underlying neural and biomarker mechanisms of compulsivity, it is necessary to measure neural aspects and biomarker aspects of the fronto-striatal circuits at two time poins, i.e. pre- and post-intervention.

Children of 6 years (ASD) or 8 years (OCD) -17 years will be included in this study, since these disorders have their most typical manifestation in childhood and early adolescence, and we examine them as these disorders are developing over childhood and adolescence (DSM 5, ICD 10).
Participants will undergo a total of (up to) 10 visits (incl. phone visit; examination, interviews, questionnaires, neuroimaging (in subgroups; MRI/ MRS assessments). If children and adolescents show any resistance the procedures will be stopped immediately. All centres involved have extensive experience with the type of research we are proposing in this protocol; potential adverse events have to be considered and special risks associated with the medications proposed in this kind of reseach. However this compound has earlier been used and investigated (at minimum in an open-label exploratory way), both in adult and paediatric patient populations, partly in other somatic or psychiatric conditions/disorders. Memantine has regulatory approval for Mb. Alzheimer in various countries, for many years.

The anticipated scientific merits justify the proposed study. There will potentially be a therapeutic benefit for the participants (depending on the balance of clinical effect/effectiveness and adverse events (per patient)) both on the individual and the group level; an assessment of the risk/benefit ratio will continuously be performed. In case of clinically/ethically inacceptable burdens or risks, single patients will be discontinued from the study, or the entire study may be stopped (also based on consultations with sponsor and scientific advisory board).

Contacts

Public
Radboudumc, Donders Institute of Brain, Cognition and Behavior

Kapittelweg 29
Nijmegen 6525 EN
NL
Scientific
Radboudumc, Donders Institute of Brain, Cognition and Behavior

Kapittelweg 29
Nijmegen 6525 EN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

ASD and OCD inpatients or outpatients
Age 6 (ASD) or 8 (OCD) untill 17;9 years at initial inclusion
CGI-S score >/<= 4 (moderately ill) at baseline visit

Exclusion criteria

Body weight < 20kg at baseline (BL)
Contra-indications for memantine, according to the Summary of Product characteristics (SPC)
Subject has a documented allergy, hypersensitivity, or intolerance to memantine
Subject has a lactose intolerance

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2017
Enrollment:	48
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-003080-38-NL
CCMO	NL52498.091.15