D-cycloserine (DCS) enhancement of exposure therapy in panic disorder with agoraphobia: a randomized controlled trial.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON34605

Source
ToetsingOnline

Brief title
D-cycloserine enhancement of exposure therapy

Condition

- Anxiety disorders and symptoms

Synonym
panic disorder with agoraphobia/panic attacks with phobia in open spaces

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Utrecht

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: agoraphobia, behavioral therapy, D-cycloserine, panic disorder

Outcome measures

Primary outcome

- PDSS scores (the Panic Disorder Severity Scale, Shear et al. 1997), measure will be taken before sessions 4 and 8, after session 12 and after 3 and 6 months follow up.

- SUDS scores (the Subjective Unit of Distress Scale, Wolpe 1969), measured weekly during the session.

Secondary outcome

De secondary outcome measurements will be taken before sessions 4 and 8, after session 12 and after 3 and 6 months follow up:

- Fawcett side effects checklist (Fawcett, 1987).

- Positive and Negative Affect Shedule (PANAS).

- Mobility Inventory (MI; Chambless, 1985).

- Agoraphobis Cognitions Questionnaire (ACQ; Chambless, 1985)

- Beck anxiety Inventory (BAI; Becl. 1990)

- EQOL (Quality of Life; WHOQOL Group, 1996).

- Beck depression inventory II (BDI-II, 1987).

- Outcome questionnaire (OQ).

- Body symptoms Questionnaire (BSQ,Chambless, 1985).

- Sheenhan Disability Scales (SDS; Sheehan, 1998).

- TiC-P (Hakkaart-van Rooijen, 2002)

- The degree of extinction during the extinction task.

Study description

Background summary

Panic disorder with agoraphobia (PD+AGO) is one of the most prevalent disorders in mental health care. Currently, behavior therapy (exposure therapy) is the treatment of choice, either alone or in combination with antidepressiva (SSRI's). Although exposure therapy has proven to result in symptom reduction in about 60% of the patients, a significant number of individuals fails to respond sufficiently to treatment.

Procedurally, exposure therapy is based on extinction of conditioned fear. Recent work in rodents and humans has demonstrated that acute treatment with D-cycloserine (DCS, a partial NMDA receptor agonist) enhances the learning and memory processes underlying extinction of fear. It is of great interest to study whether addition of DCS to exposure therapy in patients with an anxiety disorder leads to improvement of treatment effect, speed of exposure therapy and/or (as a consequence) diminished costs.
In patients with another anxiety disorder (the obsessive compulsive disorder) the first clinical trials strongly suggest that DCS, administered either 1 hour before or directly after exposure therapy, enhances the effect of the therapy in the first 5-6 sessions. In panic disorder (the 'model' anxiety disorder) DCS has barely been investigated, but results of the first study of enhancement with DCS of interoceptive exposure to panic sensations suggest enhanced treatment effect and higher remission rates in patients treated with DCS.
This study aims at extending current knowledge of exposure therapy enhancing effects of DCS in PD+AGO.

Study objective

The first aim of the study is to investigate whether DCS addition to exposure therapy enhances symptom reduction in PD+AGO.
The second objective of the study is to establish the optimal timing of administration of DCS (30 minutes before or directly after exposure therapy).
The third objective is to study the fear extinction enhancement of DCS using a neuropsychological paradigm.
The fourth objective is, from a health economic perspective, to establish cost-effectiveness of DCS.

The hypotheses are that improvement will occur at a faster rate, with addition of DCS, which will result in less therapy sessions needed and thus cost reduction.

Study design

This double blind placebo controlled trial involves patients with PD+AGO, randomized to treatment with either placebo, or single fixed dosages of 125 mg DCS during 6 sessions of a 12 session program of ET. The exposure therapy consists of a total of 12 sessions of 90 minutes. The first session is an introduction session. The study medication is administered before and after sessions 2-7, followed by 5 'regular' sessions. DCS is administered either 30 minutes before or directly after the exposure session. Thus patients with PD+AGO will be randomly allocated to 1 of 3 possible conditions. Patients in condition 1 will receive DCS before and placebo after ET. Patients in condition 2 will receive placebo both before and after ET. Patients in condition 3 will receive placebo before and DCS after ET.
For patient recruitment and inclusion, departments will collaborate with the anxiety outpatient clinic of GGZinGeest Amsterdam, GGZ Meerkanten and GGZAltrecht. We aim to include 72 patients, because we expect this is sufficient to include a minimal of 60 patients that fulfilled the study and can be used in analyses.
A baseline measurement takes place to determine all in- and exclusion criteria and to measure baseline anxiety levels to measure treatment effects.
The treatment effect on anxiety symptoms will be measured during each sessions (using a 5 minutes questionnaire).
Several measurements are planned to measure effects of treatment on anxiety symptoms and other outcome variables as other symptoms, possible side effects of DCS, the use of health care and costs, quality of life, work and loss of productivity. These measurements take place before sessions 4 and 8, after session 12 and after 3 and 6 months follow up. The measurements consist of questionnaires and one extinction task on the computer (during 10 minutes).
Extinction task: This task will be administered at the location of the therapy, before session 4. To determine how DCS facilitates the process of extinction, a version of the experimental task described by Engelhard et al (2009) will be used. We assume that patients are already conditioned for agoraphobic stimuli. An unconditioned stimulus is offered; a white noise of 500 ms, 95 dB. The loudness of this tone has been tested by Engelhard et al (2009) and has been proved to be well tolerated. Coupled with the tone (using a headphone) agoraphobic and neutral words will be offered (using a laptop). These words will NOT be followed by the noise and participants are asked to fill in their expectancy of hearing the noise. Half way the experiment the tone will be repeated to reinstate expectancy. The decrease of the expectancy will be measured (extinction) and our hypothesis is that DCS facilitates the speed of extinction.

Intervention

All patients receive exposure therapy (following a protocol) and part of the patients will get additional study medication (DCS), the other part placebo.

Study burden and risks

This study can make a contribution to a better understanding of how and with what kind of treatment panic disorder with agoraphobia could be treated better. It is expected that this study brings little harm to the patients. The only burden is that patients will be requested to invest some time for extra measurements.
Risk for adverse effects of DCS are low. Research to date has shown that there are minimal side effects at this dosage, as no side-effects have been reported to date.

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

- adult patients (between 18 and 55 years old) with panic disorder with agoraphobia (PD+AGO), according to DSM IV diagnoses as established using a standardized interview.
- patients are referred to the outpatient clinic of one of the three participating centers.

Exclusion criteria

Patients with
- comorbid psychiatric disorder (severe major depressive disorder, bipolar disorder, psychosis, dependence and/or abuse of alcohol/drugs during the past three months)
- mental deficiency
- inability to adequately read or speak Dutch
- (a history of) neurological disease (i.e. neurovascular disease, movement disorders, seizures, dementia), renal or liver abnormalities
- a history of allergies, adverse reactions or rash on medication
- currently taking benzodiazepines during the day since benzodiazepines might hamper therapy effect (use of stable dosage of evening medication is allowed)
- pregnancy or breastfeeding at the time of the study (in case of possible pregnancy, a pregnancy test will be offered)
- use of isoniazide
- use of variable dosages of antidepressiva (SSRI's or TCA's). (The use of a fixed dosage is NOT an exclusion criterium, but will be registered)
- a unsuccessful evidence based behavioral therapy for panic disorder during the past 12 months (therapy resistant patients)

Study design

Design

Study phase:	3
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):	06-10-2010
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Seromycin
Generic name:	D-cycloserine

Ethics review

Approved WMO Date:	13-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-09-2010
Application type:	First submission
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	2050
EudraCT	EUCTR2010-021198-35-NL
CCMO	NL32820.041.10