Internet-based cognitive behavior therapy in combination with D-Cycloserine for Obsessive Compulsive Disorder: A double blinded randomized controlled trial

Product: D-Cycloserine (50 mg)
EudraCT Number: 2011-002819-28
Sponsor: Christian Rück, Stockholms Läns Landsting
Principal Investigator: Christian Rück
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## Protocol Summary

**PROTOCOL IDENTITY AND OBJECTIVES**

**EudraCT Number:**

**Protocol Title:** Internet-based cognitive behavior therapy in combination with D-Cycloserine for Obsessive Compulsive Disorder: A double blinded randomized controlled trial

**Trial Objectives:**
Primary aim is to investigate whether D-Cycloserine gives incremental effects to ICBT in terms of reduced OCD symptoms. Secondary aims are to a) replicate previous findings in that DCS fastens the effects of CBT, b) correlate the fastened effect to overall treatment adherence and c) investigate gene variation and therapeutic factors as predictors of symptom severity, symptom type and treatment response.

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**INVESTIGATIONAL MEDICINAL PRODUCTS [1]**

**Test Product:** D-Cycloserine

**Pharmaceutical Form:** 3-Isoxazolidinone, 4-amino-, (R)- (Formula: C3H6N2O2)

**Route of Administration:** Orally

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**METHODOLOGY**

**Trial Design:** Double blinded randomized controlled trial

**Dose/Duration:** 5 capsules of 50 mg D-Cycloserine or placebo. 1 pcs per week for 5 weeks. All participants also receive Internet-based cognitive behavior therapy for 12 weeks.

**Primary Endpoint:** Change from W0-W13 and 3-months follow-up.

**Efficacy Parameters:** Y-BOCS clinician rated.

**Safety Parameters:** Adverse Events assessed weekly via the internet and also at post-treatment and at 3-months follow-up using face-to-face clinician assessments.

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**POPULATION OF TRIAL SUBJECTS**

**Description of Trial Subjects:** Fulfilling diagnostic criteria of OCD not associated with hoarding.

**Number of Subjects:** 128

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**TRIAL TIMETABLE**

**First Subject In:** April 2012

**Last Subject In:** October 2013

**Last Subject Out:** April 2014
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APL</td>
<td>The Swedish pharmacy productions and laboratories</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
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<tr>
<td>CBT</td>
<td>Cognitive behavior therapy</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical global improvement</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DCS</td>
<td>D-Cycloserine</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders 4(^{th}) edition</td>
</tr>
<tr>
<td>DUDIT</td>
<td>Drug User Disorders Identification Test</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>Euroqol</td>
</tr>
<tr>
<td>ERP</td>
<td>Exposure with ritual prevention</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICBT</td>
<td>Internet-based cognitive behavior therapy</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Products</td>
</tr>
<tr>
<td>KTA</td>
<td>Karolinska trial alliance</td>
</tr>
<tr>
<td>LV</td>
<td>Swedish medical products agency</td>
</tr>
<tr>
<td>MADRS-S</td>
<td>Montgomery Åsberg Depression Rating Scale – Self report</td>
</tr>
<tr>
<td>MPA</td>
<td>Medicinal Product Agency</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl-D-Asparte</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>OCI-R</td>
<td>Obsessive compulsive inventory - revised</td>
</tr>
<tr>
<td>SADR</td>
<td>Serious Adverse Drug Reaction</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SCID-I</td>
<td>Structured Clinical Interview for DSM-IV</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>TC</td>
<td>Treatment credibility</td>
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<tr>
<td>TIC-P</td>
<td>Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry</td>
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2 Administrative Information

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3 Background Information

Obsessive Compulsive Disorder (OCD) is a chronic condition characterized by obsessions and/or compulsions (e.g. fear of dirt, need for symmetry, compulsory checking), lowered quality of life, a large economic burden, and social isolation [2]. The lifetime prevalence is estimated to 2-3% [3]. First line treatments are serotonin reuptake inhibitors and cognitive behavior therapy (CBT). The active mechanism in CBT, exposure training, i.e. the patient stays in an anxiety provoking situation and stays there until the anxiety decreases, is based on fear extinction. When doing exposure of the feared stimulus repeated times, fear extinction takes place [4].

Although there is substantial evidence for the effectiveness of CBT, there is limited access to CBT therapists [5]. Evidence-based treatments are therefore not accessible for most OCD patients and it is essential to develop more time- and cost-efficient treatment delivery. Self-help treatments have the potential to be more accessible to patients. Internet-based CBT (ICBT) is a type of self-help treatment where the patient logs on to a website and works with written self-help material and homework assignments. The patient’s work with the treatment is supported by regular contact with an online therapist. The main function for the therapist is to give support through clarifying information, reviewing progress, giving the participants feedback on homework assignments and gradually giving the participants access to the treatment steps. For example, a patient with OCD who undergoes ICBT will learn about obsessions and compulsions, about the autonomous nervous system and how rituals and avoidance leads to more anxiety. Each text chapter is examined by answering questions and the patient works cooperative with the therapist in making the treatment components relevant to the patient’s everyday life. The next step in the treatment is to identify a hierarchy of fear-evoking situations and then to enter situations (exposure) at the low end of the hierarchy and not doing any rituals. This is called “exposure with response prevention” (ERP) and is done on a regular basis until the fear has attenuated. The patient makes assessments after each exposure and receives feedback from therapist. The therapist contact is limited to 10-15 weeks and usually takes about one fourth of therapist time per week compared to traditional therapy. The treatment content is not different from regular CBT but the way of delivery is what differs. ERP is never done online or in virtual reality and the treatment could be described as an Internet-based therapist-guided in vivo-exposure. One advantage of ICBT is that the text material, work sheets, self-rating questionnaires and therapist contact is integrated into one single system. ICBT has been found to be effective in randomized controlled trials in a wide range of psychiatric and medical problems [6-9]. Other possible advantages of such treatment format are increased accessibility and potential stigma reduction [10].

Our research group has developed an ICBT treatment for OCD. In a first pilot study (n=23) [11], significant in-group effects were observed with large effect sizes ($d = 1.56$). These results were
replicated in an Australian study [12]. In a subsequent RCT by our research group (n=101) [13], large between group effect sizes ($d = 1.12$) were found between ICBT and attention control. These effects are similar to those in traditional face-to-face therapy trials. Hence, ICBT is a promising treatment alternative for OCD and also has capacity to treat higher number of patients compared to face-to-face treatment because of the minimal therapist input in ICBT.

D-Cycloserine (DCS) is a treatment for Tuberculosis but has also shown to be an effective adjunct to CBT for anxiety disorders due to its N-methyl-D-asparte (NMDA) receptor partial agonistic properties. The NMDA-receptor has been shown to play a crucial role in fear extinction. The active treatment mechanism here is believed to be that DCS increases the neuroplasticity and consolidation of fear extinction, thereby enhancing the effect of CBT [14]. Several double blinded RCT: s have shown that DCS combined with CBT fastens treatment response compared to CBT + placebo [15]. Three RCT: s have been conducted with DCS + CBT for OCD. One study [16] found that CBT + DCS gave faster treatment response but no post treatment difference between the groups. Another study by Kuschner et al. [17] (n=30) found significant between group effect sizes at session 4 with lower OCD symptoms in the CBT + DCS group. The number of dropouts in the DCS group was substantially lower with 6% compared to placebo group (35%). In another study by Wilhelm et al. [18] the participants (N=23) received 10 CBT sessions with DCS vs. CBT + pill placebo. Significant between group effects of OCD symptoms were observed after half the treatment but these effects did not sustain at post treatment. To summarize, several studies has shown that DCS enhances more rapid treatment effects in OCD but these effects level out at post treatment. However, none of these studies have had sufficient power to detect significant between group effect sizes in the medium range at post treatment. In addition, no study has previously investigated DCS in combination with remote treatment such as ICBT.

There are no reported side effects of ICBT. ERP is associated with higher levels of anxiety but this anxiety decreases after repeated attempts (fear extinction). In a recently conducted RCT, we found between group effect sizes (OCD symptoms at post treatment) of 1.12 (in group effect sizes were 1.55) compared to attention-control, indicating that ICBT is a potent treatment. We scanned for adverse events during this trial but found no significant side effects of the treatment compared to controls. Previous trials with DCS using doses 25-125 mg have reported little or no side-effects of DCS compared to placebo [15, 17-19]. The doses of DCS in combination with CBT are about 10% of doses for Tuberculosis. One potential danger could be that DCS would produce reversed effects i.e. DCS could enhance fear learning instead of fear extinction. One study reported facilitation of reconsolidation of fear if given prior to a single recall trial but after using several recall trials it instead facilitated extinction [20]. No other published reports have reported any reversed effects of DCS.

4 Objectives

4.1 Primary Objective

The primary aim with the study is to investigate whether DCS gives incremental effects to ICBT in terms of reduced OCD symptoms at post-treatment and follow-up.

4.2 Secondary Objective

Secondary aims are to a) replicate previous findings in that DCS fastens the effects of CBT, b) correlate the fastened effect to overall treatment adherence and c) investigate gene variation and therapeutic factors as predictors of symptom severity, symptom type and treatment response.
5 Endpoints

5.1 Primary Endpoints
The clinician rated Y-BOCS total score [21] (expressed as the change from baseline to last post-baseline value on W0-W13 period and also at 3-month follow-up) will be used to test the superiority of DCS as adjunct to ICBT compared to ICBT + placebo on OC symptoms. Long-term follow-up will also be assessed at 12 and 24 months after treatment completion.

5.2 Secondary Endpoints
- Obsessive Compulsive Inventory – Revised (OCI-R) [23]. Baseline, post-treatment and follow-up.
- Montgomery Åsberg Depression Rating Scale – Self report (MADRS-S) [24]. Baseline, post-treatment and follow-up.
- Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TIC-P) [25]. Baseline, post-treatment and follow-up.
- Euroqol (EQ-5D) [26]. Baseline, post-treatment and follow-up.
- Global Assessment of Functioning (GAF) [27]. Baseline, post-treatment and follow-up.
- Clinical Global Impression (CGI) [28]. Baseline, post-treatment and follow-up.
- Remission status according to the Structured Clinical Interview for DSM-IV (SCID-I) [29] criteria for OCD. Baseline, post-treatment and follow-up.

5.3 Predictors
- Genetic variation
- Treatment Credibility (TC) [30]
- Working Alliance Inventory (WAI) [31]

6 Design

6.1 Outline
Experimental design with two groups, pre- and post assessment and also follow-up at 3, 12 and 24 months. Independent variables are group and time. All patients receive ICBT for 12 weeks. The participants are randomized (1:1) to either receive 50 mg DCS or placebo five times during five weeks.

6.2 Assessments and Procedures
For more information, see investigational schedule in section 19.1.
6.2.1 Internet pre-selection screening

Participants can be self-referred or referred by a clinician. Interested participants do an Internet-administered screening on an encrypted webpage using the Y-BOCS self rating [22], OCI-R [23], MADRS-S [24], Alcohol User Disorders Identification Test (AUDIT) [32], Drug User Disorders Identification Test (DUDIT) [33] and also give general background information (demographical data, phone number etc.). Written information about the study is given including objectives, benefits, risks and requirements imposed by the study, as well as the nature of the study products.

6.2.2 Telephone interview with a psychologist (pre-selection screening)

A psychologist calls the participant and conduct a structured clinical interview including the diagnostic criteria for OCD according to the SCID-I [29] and also Y-BOCS checklist (clinician version) [21]. The aim of this interview is to preliminary assess inclusion criteria and rule out exclusion criteria. Selection to the next step is done in discussion with a psychiatrist. Information is also given over the phone by the psychologist about the study protocol.

6.2.3 Psychiatrist visit (Screening)

If the participant fulfills selection criteria, he/she meets a psychiatrist at the Karolinska University Hospital in Stockholm in Solna or in Huddinge. The aim of this psychiatrist visit is to a) verify diagnosis, b) exclude other possible medical causes, c) decide on inclusion/exclusion and d) assess OCD severity level (baseline assessment W0). The psychiatric interview includes Mini-International Neuropsychiatric Interview (MINI) [34] and SCID-I (OCD criteria) [29] and Y-BOCS (clinician rating version) [21]. If included to the study, pre-treatment assessment is conducted by the psychiatrist using the GAF [27], Y-BOCS (clinician rating version) [21] and CGI [28]. Careful information is also given by the psychiatrist about the study protocol and how the DCS/placebo should be taken. Informed consent is signed and gathered during this visit.

6.2.4 Inclusion and randomization

If included, the patients meet a licenced GCP-trained nurse within a few days after the psychiatrist visit. The nurse administers 5 capsules of DCS or capsule placebo. The participant also receives written information about capsule intake ordination and a telephone number if the participant has any questions or to report AE. Randomization procedure and administration blindness will be performed by APL using block randomisation on 1:1 ratio.

6.2.5 Mid treatment assessment

WAI [31] and TC [30] are assessed at mid treatment (W6) via Internet to investigate predictors of treatment outcome. Y-BOCS clinician version [21] is also assessed via telephone by a clinician at mid-treatment (W6).

6.2.6 Weekly assessments

Y-BOCS self-rating [22] is assessed weekly in the treatment platform.

6.2.7 Post treatment assessment

Psychiatrist visits within 14 days after treatment (W13) using the GAF [27], Y-BOCS (clinician rating version) [21] and CGI [28]. Remission status is determined using the SCID-I; [29] and
MINI [34]. Secondary outcomes are conducted on the internet using Y-BOCS self-rating [22], OCI-R [23], MADRS-S [24], TIC-P [25] and EQ-5D [26].

6.2.8 Follow-up assessments
Face-to-face interview with a clinician at 3, 12 and 24 months follow-up. Blinding is broken after all participants have completed the 3-month follow-up assessment. Secondary outcomes are conducted on the internet using the Y-BOCS self-rating [21], OCI-R [23], MADRS-S [24], TIC-P [25] and EQ-5D [26].

6.3 Measures to minimize bias
The following procedures have been taken to avoid bias:
- This is a double-blind study and the study drugs will be of identical appearance in order to protect the blinding toward the participant and the investigator. As there are no obvious side effects associated with the drug, the placebo capsules will be passive.
- The treatment (DCS or placebo) is assigned at inclusion by balanced randomization. The structure responsible for designing and constructing the randomization list in blind will be the KTA.

7 Selection and Withdrawal of Subjects

7.1 Inclusion Criteria
- Outpatients
- Male or female
- ≥ 18 years
- Primary diagnosis of OCD according to the DSM-IV-TR.
- Signed informed consent
- Have regular access to a computer with internet access and skills to use the web
- Have received information about the need of using contraception

7.2 Exclusion Criteria
- Pregnancy or breast feeding
- Patients unlikely to cooperate fully in the study
- Patients not able to read or understand the basics of the ICBT self-help material
- Psychotropic medication changes within two months prior to treatment
- Completed CBT for OCD within last 12 months
• Y-BOCS [21] < 16 at Psychiatrist visit (6.2.3)pi
• OCD symptoms primarily associated with hoarding.
• Other primary axis I diagnosis according to the Mini-International Neuropsychiatric Interview (MINI) [34]
• Ongoing substance dependence
• Lifetime bipolar disorder or psychosis
• Suicidal ideation
• Axis II diagnosis that could jeopardize treatment participation
• Serious physical illness that will be an obstacle in ICBT and DCS
• Other ongoing psychological treatments that could affect OCD symptoms
• Epilepsia
• Renal impairment
• Hypersensitivity to D-Cycloserine
• Porphyria
• Chronic Alcoholism

7.3 Criteria for Withdrawal

Criteria for mandatory discontinuation of treatment:
• Consent withdrawal by the patient
• High suicide risk according to investigator’s judgment or any suicide attempts during the study whatever its severity
• Worsening of OCD symptoms, which in the opinion of the investigator requires an adaptation of treatment not compatible with the protocol or requires hospitalization.
• Pregnancy. The participant will be allowed to continue ICBT but without medicine intake.

Other possible reasons for premature discontinuation of treatment
• Any adverse event or circumstances justifying the discontinuation of the treatment in the investigator’s opinion. If the adverse event is considered to be uniquely caused by DCS/placebo, the participant will be allowed to continue ICBT but without medicine intake.
• Treatment failure
• Protocol deviation which jeopardizes the patient’s safety
• Patient lost to follow-up: When the investigator has no news from the participant, he/she must make every effort to contact him/her, to establish the reason for discontinuation of
treatment, and to suggest the participant comes to an end-of-study visit. If all such attempts to contact the participant fail, the investigator then declare the participant lost to post-treatment assessment the investigator should document all these attempts in the corresponding medical file.

7.4 Subject Log
If possible, the investigator must record the reason and the exact time of the premature discontinuation of treatment in the case report form (CRF). If more than one reason is given, the investigator must indicate the main reason. In case of treatment discontinuation for any reason between visits W0 and W13, and end-of-study visit should be done with all the assessments planned for the visit W13 as early as possible after the study treatment discontinuation.

8 Treatment

8.1 Description of Investigational Medicinal Products

8.1.1 ICBT Treatment
Both groups receive the same ICBT treatment. Treatment starts within seven days after the psychiatrist visit. Both therapists and participants are blinded to DCS/placebo randomization. The psychological treatment is 12 weeks of ICBT for OCD. This treatment has been evaluated in two previous trials with large in-group and between group effect sizes. The treatment is divided in 10 steps (modules). Module 1-4 focuses on behavior analysis and to develop a treatment plan based on ERP principles. It is possible to proceed to the next module within a few days but should not take longer than one week. All participants have to proceed through module 1-4 consecutively in order to proceed to the active treatment (ERP). Module 5-10 focuses on doing ERP. Each module focuses on certain types of ERP and gives more in depth knowledge of those exercises.

8.1.2 DCS/placebo treatment
The prescribed intake is 5 capsules, once per week for five weeks. The participant either receives 50 mg of DCS or a placebo capsule. As there are no reported significant side effects [17, 18] associated with this low dose of DCS (≤125mg), the placebo capsule is passive i.e. does not actively create any side-effects. Module 1-4: No DCS intake during this period. The participant progress in his/her own pace through module 1-4 but is advised not to take more than 28 days for module 1-4. Module 5-10: One module per week. One capsule of DCS/placebo per week for 5 weeks. DCS/placebo intake is carefully planned together with the therapist. The participant conducts one ERP in vivo session per week with DCS/placebo as an adjunct. The participant takes one capsule within 1 hour before ERP. The overall treatment starting point for DCS varies between participants, as it is possible to do module 1-4 in a faster pace than one module per week. Capsule intake and treatment progression is highly controlled during ERP (module 5-10). As the treatment is 12 weeks, the participant has additional room for 2 weeks of delay. If the participant has taken all 5 DCS/placebo capsules for 5 weeks, the rest of the treatment period is devoted to continued ERP but without DCS/placebo.

A warning system in the treatment platform warns the therapist if the participant is behind the treatment schedule of completed modules. If the participant has not logged in to the treatment platform for 7 days, the therapist sends a text message or calls the participant.
8.2 Packaging, Labeling, Storage and Handling of Investigational Medicinal Products

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>ICBT</th>
<th>DCS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internet-delivered CBT in self-help format</td>
<td>Capsule DCS 50 mg</td>
<td>Placebo capsule</td>
<td></td>
</tr>
<tr>
<td>Unit dosage</td>
<td>Access to therapist mo-fri 08-17.</td>
<td>50 mg</td>
<td>-</td>
</tr>
</tbody>
</table>

8.3 Treatment Assignment
Participants are randomized consecutively using block randomization on a 1:1 ratio. A document with all randomizations will be established before inclusion (e.g. inclusion 1: TX, inclusion 2: TX, inclusion 3: Ctrl etc.). Block size of each randomization will be blinded to the investigator by APL.

8.4 Blinding and Code Breaking
Sealed envelopes will be sent with the DCS/Placebo treatments and given to the investigator. The envelopes should be kept in a safe place and accessible to any person authorized to unblind. A decoding list containing the treatment codes will be kept at the clinic.

The code for any study participant should only be broken by the investigator or authorized person if it is absolutely necessary to ascertain the type of treatment given.

The circumstances under which the code may be broken are life-threatening emergencies, for which the choice of therapy may depend on the treatment received by the patient. If so, the investigator must write his name, signature, date, the number of the participant concerned and reason for breaking the code on the code envelope.

All information concerning adverse drug reactions, drug interactions are given in the investigator’s brochure.

8.5 Concomitant and prior medication
Parallel psychotropic medications are allowed but must be stable for at least 2 months before inclusion. The participants will be instructed to avoid alcohol consumption during the treatment and also concurrent seizure threshold-lowering medications such as bupropion or tramadol.

8.6 Compliance to Treatment
DCS adherence will be monitored by the psychologist after each intake, which the patient and the psychologist plan together in the ICBT treatment after module 4. The monitoring will be conducted with written reports in the treatment platform. In addition, the capsule dosettes will digitally log the time each capsule is retrieved from the box (Aardex MEMS dosette boxes) [35]. The participant will also have the opportunity to retrospectively report at post-treatment if he/she had give wrong information during the treatment. Intake is written by the therapist in the CRF.

8.7 Product Accountability
DCS will be supplied from APL (Prismavägen 2 Kungens Kurva, Sweden, tel: 010-447 96 00). Treatment management will be under responsibility of the investigator.

The therapeutic DCS units will be sent to the investigator and should be stored in a secure area with restricted access. The expiry date will appear on each box and each label.

The investigator will acknowledge the receipt of therapeutic units by signing the shipping form.
The DCS treatments will be dispensed by the investigator in accordance with the study plan and following dispensing methods described in section 22.2. Drug accountability will be responsibility of the investigator. Remaining treatments will be collected by APL for storage and later on destruction.

8.8 Continuation of Treatment

Patients will not be treated with DCS after W12 but are recommended to continue ERP in accordance with the CBT model for OCD. If a participant decides to discontinue DCS/placebo treatment, he/she has still the opportunity to continue the ICBT treatment. If a participant is behind the treatment schedule (e.g. starts exposure at week 10) and has not the possibility to take all 5 capsules before the end of the treatment period (12 weeks), he/she will return remaining capsules at the psychiatrist post-treatment visit. Blinding will be broken when the last subject has completed the 3-month follow-up assessment (results will be published). The whole trial will end when the last subject has completed the 24-month follow-up assessment (separate articles investigating the long-term effects of DCS).

9 Assessment of Efficacy and Safety

9.1 Clinical Efficacy Assessments

The primary outcome measure is the clinician-administered Y-BOCS [21], which is regarded as the gold standard for assessing the severity of OCD symptoms [36]. Y-BOCS comprises 10 items, rated on a 5-point Likert scale ranging from 0 (no symptoms) to 4 (severe symptoms). The total score ranges from 0 to 40 and consists of two sub scores for compulsions (range 0 to 20) and obsessions (range 0 to 20). Y-BOCS has excellent inter-rater reliability and moderate to good internal consistency [21]. The Clinical Global Impression Scale [CGI-I; 37] and Global Assessment of Functioning [27] is used to measure global improvement. Both the clinician version of Y-BOCS as well as CGI is administered at baseline and post-treatment by a physician or by a psychologist at 3, 12 and 24-month follow-up.

The following scales are used as self-ratings scales, which the participant fills out via the Internet:

- The Y-BOCS self-rating scale. This questionnaire is assessed weekly to monitor treatment progression. One study found a correlation between the computer and clinician administered Y-BOCS of .88 [22].

- Obsessive-Compulsive Inventory – Revised: The OCI-R is a 18 items self-rating scale, measuring six different symptom dimensions [23]. The OCI-R total score has high test-retest reliability (alpha values from .81 to .89) and high sensitivity to change, in relation to the Y-BOCS [38].

- Montgomery Åsberg Depression Rating Scale – Self report (MADRS-S): The MADRS-S is a 9-item questionnaire assessing depressive symptoms. The MADRS-S has good test-retest reliability (.80 - .94) and correlates (r= .87) with the Beck Depression Inventory, indicating acceptable convergent validity [39].

- Euroqol (EQ-5D): The euroqol (EQ-5D) is used as a generic measurement of global functioning and quality of life [40]. The EQ-5D is non-disease specific and measures five health domains of importance to quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [41]. The measure has good psychometric
properties including acceptable test-retest reliability over 7 to 10 days (intraclass coefficient= .82 - .83) and acceptable convergent validity [42].

- Trimbos and Institute of Medical Technology Assessment Cost Questionnaire for Psychiatry (TIC-P): TIC-P [43] measures monthly number of health care visits, other health-related help, work absenteeism, work cutback and household cutback.

- Treatment credibility scale (TC): TC [44] assesses how credible the participants perceive the treatment to be and how much the expect that they will improve from the treatment.

- Working alliance inventory (WAI): WAI [31] is a 14 item questionnaire that assesses the therapeutic relationship.

9.2 Clinical Safety Assessments
Safety measurements performed for each face-to-face visit and also weekly using the adverse event questionnaire via the Internet (as indicated in “Investigational schedule“ in section 19.1)

9.3 Laboratory Assessments
Participation in DNA analysis is voluntary and does not affect participation in the treatment study. Participants leave blood sample for DNA analysis. Patient consent and information is given before the psychiatrist visit. Genotyping is made in collaboration with prof. Martin Schalling’s lab at CMM, Karolinska Institutet. We also collect RNA in blood to study gene expression and plasma to study proteins.

9.4 Laboratory Safety Assessments
A research nurse takes blood sample immediately after the psychiatrist visit if included to the study. Blood samples are stored encoded in a separate freezer with a temperature below -20 degrees Celsius.

10 Proceedings for Adverse Events

10.1 Definition of Adverse Events

10.1.1 Definition of Adverse Events
An Adverse Event (AE) is any untoward medical occurrence in a subject administered Investigational Medicinal Products [1] and which does not necessarily have a causal relationship with this product. An AE can be any unfavorable and unintended sign, abnormal laboratory finding, symptom or disease temporally associated with the use of IMP, whether or not related to the product.

10.1.2 Definition of Adverse Reactions
Each AE is to be classified by the investigator as related or not related to the IMP. An Adverse Reaction (AR) is a noxious and unintended medical response to a medical product related to any dose. For an AE to be an AR the suspected association between the product and the unwanted medical condition should be at least a reasonable possibility.
10.1.3 **Definition of Serious Adverse Events**
Each AE is to be classified by the investigator as serious or non-serious. Seriousness is not defined by a medical term; it is a result or an outcome. An AE is defined as a Serious Adverse Event (SAE) if it:
- results in death
- is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect

10.1.4 **Definition of Suspected Unexpected Serious Adverse Reactions**
Each SAE that is at least possibly related to IMP is to be classified by the investigator as expected or unexpected. A SAE that is at least possibly related to IMP, and unexpected, is defined as a Suspected Unexpected Serious Adverse Reaction (SUSAR). It is expected if it is already known from earlier trials or is mentioned in relevant documents. The reference security information of the IMP can be found in the approved SPC [45].

10.2 **Assessment of Adverse Events**
AE is assessed at each clinician visit and in the treatment platform. If any AE is recorded in the treatment platform, the therapist will print out the information and give it to the investigator.

10.2.1 **Assessment of Intensity**
Each AE is to be classified by the investigator as mild, moderate or severe.
**Mild:** Acceptable. The subject is aware of symptoms or signs, but they are easy tolerated.
**Moderate:** Disturbing. The AE is discomfort enough to interfere with usual daily activity.
**Severe:** Unacceptable. The subject is incapacity to work or to do usual daily activities.

10.2.2 **Assessment of Causality**
**Unlikely:** The event is most likely related to an etiology other than the IMP.
**Possible:** A causal relationship is conceivable and cannot be dismissed.
**Probably:** Good reason and sufficient documentation to assume a causal relationship.

10.3 **Methods for Eliciting Adverse Events**
Safety measurements performed for each clinician visit and weekly using the adverse event questionnaire via the Internet (as indicated in "Investigational schedule" under section 19.1)

10.4 **Reporting of Adverse Events**

10.4.1 **Reporting of Adverse Events**
All AEs will be recorded on a separate AE form in the CRF.

10.4.2 **Reporting of Serious Adverse Events**
SAEs will be reported by the investigator. Follow-up information describing the outcome of the SAE and action taken will be reported as soon as it is available. The original SAE form must be filed with the CRF.
10.4.3  Reporting of Suspected Unexpected Serious Adverse reactions
The sponsor must report all SUSARs that resulted in death or was life threatening through CION-form to LV within 7 days. Other SUSAR should be reported within 15 days. In addition will the sponsor report all SUSAR to all Principal Investigators involved in trials with the IMP.

10.5 Follow-up of Adverse Events
The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding adverse events must be written up in an Adverse Events evaluation form.

11 Statistics and Data Management

11.1 Data Management
CRF data will be imputed to a data file. Statistical analysis will be performed by the investigator and quality controlled and crosschecked by independent party.

11.2 Statistical Analysis
The primary objective is to demonstrate superiority of ICBT + DCS vs. ICBT + placebo. This is done using an ANOVA with repeated measurement to test for group * time interaction effects (two-tailed). Data will be analyzed using intention to treat methodology with a mixed models design, accounting for missing data. In our pilot study, we had 100% data on the primary outcome (clinician Y-BOCS) and the corresponding figure in the subsequent RCT, we had 99% data post-treatment and 100% data at follow-up (4 months). Hence, we expect the data loss to be low in this study as well.

The primary criterion is the Y-BOCS total score from baseline to post-treatment and also 3-month follow-up. Secondary dependent variables are Y-BOCS self-rating [22], OCI-R [23], MADRS-S [24], TIC-P [25], EQ-5D [26], GAF [27]). Remission status is assessed using the SCID-I [29].

DNA polymorphism candidates will be used as predictors of treatment outcome using a regression framework.

Treatment credibility (TC) and working alliance (WAI) will be used as predictors of treatment outcome using a regression framework.

Number of emergent adverse events under treatment, number and percentage of patients reporting at least one emergent adverse event will be described.

11.3 Determination of Sample Size
A meta analysis by Norberg, Krystal & Tolin [46] found medium effect sizes for CBT + DCS with doses similar to this trial (≤ 125mg) for patients with OCD. Assuming 80% power, the study therefore needs 128 participants to find a medium effect size (Cohen’s δ) of 0.5 (two-tailed, alpha level=.05).
12 Direct Access to Source Documents

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the ethics committee and of competent authorities to have direct access to source data and documents.

13 Quality Control and Quality Assurance

13.1 Source Data

Patient source data file will be established before the study starts. Patient data is stored in the CRF and also as computerized information at Psykiatri Sydväst. When computerized information is used, the investigator undertakes to keep printouts, which are signed and dated by the investigator and by the monitor.

13.2 Monitoring

Monitoring is conducted before, during and after the study by KTA according to ICH-GCP guidelines.

13.3 Inspection

The investigator must allow representatives of the competent authorities and persons responsible for the inspection:

- Inspect the site, facilities and material used for the study.
- To meet all members of his team involved in the study.
- To have direct access to study data and source documents.
- To consult all of the documents relevant to the study.

14 Ethics

14.1 Independent Ethics Committee

The study protocol and necessary documentation will be submitted to the regional ethics committee in Stockholm.

14.2 Ethical Conduct of the Trial (risks and benefits)

The study will be performed in accordance with the ethical principles stated in the declaration of Helsinki 1964, revised in Seoul 2008. There are no reported side effects of using DCS of lower doses than 125 mg. There are no reversed effects reported (i.e. that DCS could enhance fear learning instead of fear acquisition). Studies from rat experiments also show that DCS only enhance fear unlearning and not fear acquisition. Potential risks are that DCS could lessen the treatment efficacy (IBCT). Even if previous research studies do not suggest this we cannot exclude the possibility. If the participants have any inquiries about the treatment, he/she has the possibility to contact a therapist in the treatment platform and expect an answer within 24 hours. Data is gathered in accordance with the Swedish Personal Data Act and patients give their written consent for data storage. All participants give their written consent to the access of national data registers. OCD is associated with lowered quality of life on the sufferers. ICBT has the potential to access more OCD sufferers which are in need of evidence based treatments. If
DCS is found effective, we could further improve this treatment. We are also studying genetic variation in relationship to carefully genotyped patients that undergo ICBT. This could potentially lead to new knowledge regarding OCD and also regarding genetic variation that contributes to success in CBT. We do think that this project will contribute to the advancement of academic psychiatry and that also is likely to benefit patients in the near future.

14.3 Subject Information and Informed Consent
The investigator or a physician designated by him is to collect written consent form each participant before participation in the study. Prior to this, the investigator or delegate must inform the patient of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the study products.

One original of the informed consent will be signed by the participant and collected by the physician. The participant will receive a copy of the original signed informed consent.

15 Data Handling and Record Keeping

15.1 Case Report Forms
The investigator designates authorization to other personnel in written form in the CRF (signed by the investigator and date of signature). All changes must be signed by the investigator and authorized personnel at the clinic. Each CRF should have a copy that is stored at another location. CRF data quality is monitored by KTA.

15.2 Record Keeping
The investigator is responsible for saving all documents in readable condition in 10 years after the study has been reported to the Swedish medical products agency. The documents will be accessible for audit from authorized government agencies during this time.

16 Financing and Insurance
The Stockholm County Council (ALF) funds this study. Patients are insured by the Swedish patient and medical insurance.

17 Publication Policy
Separate plan of publications has been established.
18 Signed Agreement of the Trial Protocol

Principal Investigator
Christian Rücker, MD, PhD
M46 Internetpsykiatrienheden
SLL

Signature

Date 13 March 2012

Sponsor
Christian Rücker, MD, PhD
M46 Internetpsykiatrienheden
SLL

Signature

Date 13 March 2012
19 Appendices

19.1 Table and figure of Investigational Events

19.1.1 Table of investigational schedule

<table>
<thead>
<tr>
<th></th>
<th>Pre-selection Internet screening</th>
<th>Pre-selection Telephone interview</th>
<th>Screening: Psychiatrist visit W0</th>
<th>Nurse visit W0</th>
<th>Treatment W1-W12</th>
<th>Post-treatment: Psychiatrist visit W13</th>
<th>3-month follow-up: Clinician visit W26</th>
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19.1.2 Figure of investigational schedule

Pre-selection Internet screening:
- Y-BOCS (self-rating)
- OCI-R
- AUDIT
- DUDIT
- MADRS-S

Background information

Pre-selection telephone interview with a psychologist:
- SCID-I
- Y-BOCS (clinician version)

Previous psychological treatment

Current medical status

Face-to-face screening interview with a physician:
- SCID-I
- Y-BOCS (clinician version)

Previous psychological treatment

Current medical status

Included and randomized (N=128)

DCS/placebo is provided. Blood sample is taken by a nurse.

5 pieces of placebo over 5 weeks. Weekly monitoring of AE via Internet. Weekly symptom ratings with Y-BOCS (self rating) and one mid treatment assessment with Y-BOCS (clinician version) via the telephone.

ICBT + DCS (N=64) 12 weeks

ICBT + placebo (N=64) 12 weeks

Psychiatrist visit (W13-W14): Y-BOCS, CGI, GAF, Diagnosis (SCID-I)

Internet self-ratings (W13):
- OCI-R, MADRS-S, TIC-P, EQ-5D, Y-BOCS

Psychiatrist visit (W13-W14): Y-BOCS, CGI, GAF, Diagnosis (SCID-I)

Internet self-ratings (W13):
- OCI-R, MADRS-S, TIC-P, EQ-5D, Y-BOCS

AE assessed by the psychiatrist.

AE assessed by the psychiatrist.

3-month follow-up (+/- 2 weeks):
- Clinician visit:
  - Y-BOCS, CGI, GAF, Diagnosis (SCID-I)
  - Internet self-ratings:
    - OCI-R, MADRS-S, TIC-P, EQ-5D, Y-BOCS

AE assessed by the clinician.

AE assessed by the clinician.

3-month follow-up (+/- 2 weeks):
- Clinician visit:
  - Y-BOCS, CGI, GAF, Diagnosis (SCID-I)
  - Internet self-ratings:
    - OCI-R, MADRS-S, TIC-P, EQ-5D, Y-BOCS

Blinding is broken by KTA follow-up at 12 and 24 months, clinician visit (Y-BOCS, CGI, GAF, SCID-I) and Internet assessment (OCI-R, MADRS-S, TIC-P, EQ-5D, Y-BOCS)

Written information about the study is given including objectives, benefits, risks and requirements imposed by the study, as well as the nature of the study products.

Preliminary diagnostic interview to determine if the participant should proceed to a face-to-face diagnostic interview with a psychiatrist. Information is also given over the phone about the study.

Informed consent is collected by a physician at the beginning of the visit. Inclusion/exclusion is decided by the psychiatrist. Rules of participation and medications are given by the psychiatrist.
19.2 D-Cycloserine substance information

19.2.1 Information on ingredients:
Formula: C3H6N2O2
Chemical Name: 3-Isoxazolidinone, 4-amino-, (R)-
CAS: 68-41-7
RTECS Number: NY2975000
Chemical Family: Isoxazole
Therapeutic Category: Antibacterial (tuberculostatic)
Autoignition Temperature: n/f
ATC Code for cycloserine: J04AB01
Formula: C3H6N2O2
Molecular Weight: 102.09

19.2.2 Toxicological properties:
Oral Rat: LD50: >5 grams/kg
Oral Mouse: LD50: 5290 mg/kg
Other Toxicity Data:
Oral Guinea Pig: LD50: > 2 grams/kg
Oral Dog: LD50: > 2 grams/kg
Irritancy Data: Rabbit/eye: slight
Rabbit/skin: non-irritating
Listed as a Carcinogen by: NTP: No IARC: No OSHA: No
Other Carcinogenicity Data: No
Mutagenicity Data: The Ames test and unscheduled DNA repair test were negative
Reproductive and Developmental Effects: A study in rats at doses up to 100 mg/kg/day showed no adverse reproductive effects

19.2.3 Disposal
Dispose of waste in accordance with all applicable Federal, State and local laws.

20 REFERENCES:


13. Andersson, E., et al., *Internet-based cognitive behaviour therapy for obsessive-compulsive disorder: a randomised controlled trial (Submitted manuscript).*


