Hovedoppgave

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Norges teknisk-naturvitenskapelige universitet
Fakultet for samfunns- og utdanningsvitenskap
Institutt for psykologi

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Effect of Concentrated Exposure and Response Prevention on Symptoms of Insomnia: Results from a Randomized Clinical Trial on the Effects of D-Cycloserine for People with Difficult-to-Treat Obsessive-Compulsive Disorder

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Sammendrag

Bakgrunn: Det er økende enighet om at insomnisymptomer blant pasienter med tvangslidelse (OCD) er vanlig. Denne randomiserte kontrollerte studien undersøkte effektene av Bergen 4-dagers behandling (B4DT) på insomni i en gruppe behandlingsresistente OCD-pasienter og om D-Cykloserin forsterker effekten av behandlingen.

Metode: Pasientene som ble inkludert (N = 163) hadde enten ikke respondert eller fått tilbakefall etter tidligere behandling basert på eksponering for OCD. De ble allokert til tre grupper som mottok enten placebo, 100 mg eller 250 mg D-Cykloserin (DCS).

Resultater: Det fremkom en liten, men robust effekt av behandlingen på insomnisymptomer (d = 0.37), opprettholdt ved 3-måneders oppfølging (d = 0.38), og noe redusert ved 12-måneders oppfølging (d = 0.23). Det var ingen signifikante forskjeller mellom gruppene som mottok DCS eller placebo. Insomni påvirket heller ikke utfallet av OCD-behandlingen.

Diskusjon: Studien indikerte at OCD-behandling påvirker insomnisymptomer positivt. Verken komorbid insomni eller DCS modererte behandlingsresultatet. Pasienter med OCD og komorbid insomni bør vurderes for spesifikk insomnibehandling.

Abstract

Background: There is a growing consensus concerning the large prevalence of insomnia symptoms among patients with obsessive-compulsive disorder (OCD). This randomized controlled study explored the effects of the Bergen 4-day treatment (B4DT) on sleep difficulties in a sample of difficult-to-treat OCD and whether D-Cycloserine (DCS) augmented the effect of treatment.

Methods: Patients included (N = 163) had either not responded or relapsed following OCD treatment. They were allocated to three groups receiving either a placebo, 100 mg or 250 mg of DCS.

Results: There was a small, but robust effect of the treatment on insomnia symptoms (d = 0.37), withheld at the 3-month follow-up (d = 0.38), and slightly reduced at the 12-month follow-up (d = 0.23). No significant differences between the groups receiving DCS or placebo were found. Additionally, insomnia did not affect OCD-treatment outcome.

Discussion: This study showed that OCD treatment is associated with improvement in insomnia symptoms. Comorbid insomnia and DCS did not moderate treatment outcome. Patients with OCD and comorbid insomnia should be considered for specific insomnia treatment.

Forord

Oppgaven er skrevet i artikkelformat med tanke på mulig publisering. Arbeidet med oppgaven har vært en utfordrende reise, som vi har klart å gjennomføre med god hjelp. Først og fremst vil vi takke Stian Solem for fantastisk veiledning av to surrete karer. Det har blitt mange trivelige timer på kontoret med både humor og alvor – uten å oppgi den sanne fordelingen av disse to. Et annet navn som begge forfatterne vil trekke frem er Nils Inge Landrø. Vi kan nevne hyggelige stunder i form av fotballkamper, lunsjer, middager, viktige påminnelser, gjennomlesninger og gode tilbakemeldinger. Videre vil forfatterne også takke hverandre for et samarbeid som ikke bare har omhandlet oppgaven, men også et halvannet års langt samboerskap, to års arbeid sammen som kollokvieveiledere ved NTNU, treningspartnere, festpartnere, samt fem og et halvt års vennskap som i skrivende stund fortsetter sin gang i Oslo. I tillegg vil hver av forfatterne gi noen personlige takksigelser.

Nils: Oppgaven markerer slutten på mange nydelige år i Trondheim som ikke hadde vært det samme uten alle mine bokamerater, venner og studiefelleskapet! Spesiell takk til mamma og pappa som har inspirert og støttet meg på hele reisen, Andreas Lillebråten for trofast samboerskap hvor ingen dag var den samme, Ivar Fugle Nordhaug for nært vennskap fra første til siste blikk gjennom alle år på psykologi og selvfølgelig Tuva Bjerkebakke for å være den aller viktigste for meg i Trondheim, Oslo og alle andre steder vi skulle ende opp!

Sigurd: Jeg vil sende en takk til mor og far som jeg hverken har ringt eller besøkt ofte nok mens jeg har vært i Trondheim. Dette forordet er nok det eneste dere vil forstå i denne oppgaven, men det er ikke fordi dere er dumme, det er bare fordi dere aldri har blitt indoktrinert i akademia. Søken etter sannhet har kostet, og jeg har dessverre ingen flere takksigelser å sende ut. Dette er noe som vil endres ved en eventuell senere anledning, og jeg vender nå tilbake til menneskene. Ta meg imot, som jeg tar imot C-laget og Gamle gress.

Sigurd og Nils, Oslo 30. Januar 2024.

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Introduction

Insomnia is a condition comprised of night- and day-time symptoms affecting well-being and quality of life. Night-time symptoms include early morning wakening, disturbed sleep maintenance and delayed sleep onset, with day-time functioning characterized by fatigue, cognitive impairment and low mood (Riemann et al., 2022). The disorder is recognized in both the Diagnostic and Statistical Manual of the American Psychiatric Association, 5th revision (DSM-5, 2022), and the International Classification of Diseases, 11th revision (ICD-11, 2023), with as many as 10% of the general population fulfilling the criteria for chronic insomnia (Riemann et al., 2022). Estimates for the US show that insomnia has societal costs of around 150 billion dollars a year (Reynolds & Ebben, 2017). In clinical populations its prevalence is even higher, being a clinically significant feature of most mental disorders with 70-80% of patients showing insomnia in the acute phase of their mental illness (Palagini et al., 2022). As this link is seen across virtually all psychiatric conditions a transdiagnostic model has been suggested, showing how sleep disturbances have a negative impact on a range of neurobiological systems, which may in turn increase the development of mental illness (Harvey et al., 2011).

Patients with obsessive-compulsive disorder (OCD) are not exempt from comorbidity with insomnia. This debilitating condition, characterized by intrusive thoughts and compulsions, has a lifetime prevalence of 1-1.5% (Fawcett et al., 2020). While the link between OCD and sleep difficulties has seen relatively little research in comparison to other conditions, there is a growing literature which has shown a consistent link between sleep disturbance and OCD (Cox et al., 2020). Patients with OCD show both increases in subjectively reported sleep difficulties and objective measures like disturbances in circadian rhythms, sleep effectiveness, and total sleep time (Nota et al., 2015). One Swedish population-based cohort study reported a 7-fold increase in insomnia among patients with OCD compared to the general population (Sevilla-Cermeño et al., 2020). The causal mechanism behind this link may be explained by the transdiagnostic model. Sleep disturbances and its negative impact on various neurobiological systems lead to deficits in multiple cognitive domains (Harvey et al., 2011). One such effect is a decrease in cognitive control, shown in patients with sleep disturbances, which in turn may lead to an increase of OCD-symptoms as the obsessions “grow” without cognitive control (Cox et al., 2018). This relationship is seen as bidirectional in nature as studies have found a unique connection

between the “obsessions” domain of OCD, especially the so-called unacceptable obsessive thoughts and sleep disturbances (Timpano et al., 2014). Thus, the unacceptable obsessive thoughts may contribute to increased sleep disturbances as they keep arousal too high, while sleep disturbances weaken cognitive control so the obsessive thoughts increase.

Evidence for cognitive behavioral therapy (CBT) on concomitant sleep disturbances is inconclusive. Although one review showed a moderate effect size (d = 0.53) on sleep difficulties for treatment of anxiety disorders across 19 studies, this was based on a small number of studies and few reported the effect on concomitant sleep difficulty (Belleville et al., 2010). A newer, single study showed a modest effect on global sleep quality and sleep latency following CBT for patients with generalized anxiety disorder and panic disorder, but no effect on other sleep indices (Ramsawh et al., 2016). The authors of these studies pointed to a lack of research on the effect of treatment on comorbid sleep difficulty despite its high prevalence.

CBT treatment comes in different variations such as individual therapy, group sessions, and exposure-based treatments. One such concentrated treatment, the Bergen 4-day treatment (B4DT) is based on a combination of group therapy and individually tailored exposure training. B4DT has proven effective in multiple studies, with remission rates up to 90% at post-treatment, 70% at 3-month follow-up, with the change maintained at 1 and 4-year follow-up (Hansen et al., 2018; Hansen et al., 2019; Kvale et al., 2018). Some recent studies have tried to explore the B4DT’s effect on concomitant sleep difficulty. The first looked at a relatively small (N = 36) sample of which 70% had comorbid sleep difficulties indicating clinically significant insomnia as measured with the Bergen Insomnia Scale (BIS; Nordahl et al., 2018). The patients reported small (d = 0.26) reductions in insomnia at post-treatment and moderate reductions (d = 0.55) at follow-up. Patients with higher levels of sleep difficulties showed the largest reductions in OCD-symptoms. A newer randomized control study (RCT) employing the B4DT (N=48) showed a moderate (d = 0.53) improvement in insomnia symptoms at 3-month follow-up, compared with waiting-list and unguided self-help (Hagen et al., 2021). This effect, however, had no association with OCD-treatment outcome, so their conclusion was that insomnia symptoms were reduced following OCD treatment regardless of the treatment's effect on OCD symptoms. These preliminary findings indicated that sleep difficulties do not impair OCD-treatment and that concentrated

exposure therapy for OCD shows promise in reducing insomnia symptoms for patients with OCD with comorbid sleep difficulties. However, both studies had relatively small samples.

There have been efforts to test medications which may augment and facilitate extinction learning and extinction-related brain activation (Schade & Paulus, 2016). One such medication is DCS which works by influencing glutamatergic neurotransmission, specifically targeting N-methyl-D-aspartate (NMDA) receptors. Originally administered in larger doses as a treatment for tuberculosis, DCS has in more recent years undergone a lot of testing as a supplement medication to CBT treatment of anxiety disorders. This is because the NMDA receptors play a central role in long term potentiation and have been shown to bolster synaptic plasticity and learning (Schade & Paulus, 2016). The study presented here is based on data first published in Kvale et al. (2020) studying the effects of the B4DT on treatment-resistant OCD and whether the effects were augmented by D-Cycloserine (DCS).

A range of studies have since been conducted on the combination of DCS and forms of CBT involving extinction learning on different anxiety disorders. A meta-analysis showed a large and robust effect in animal studies (on extinction learning specifically) and a smaller yet significant effect in human studies on CBT augmented by DCS (Norberg et al., 2008). More recent meta-analyses have reported mixed results, one showing a small effect from pre- to post-treatment, not withheld at follow-up (Mataix-Cols et al., 2017), and the newest study finding effect sizes close to zero (Bürkner et al., 2017). This last meta-analysis also pointed out how more recent and high-quality studies showed smaller effects of DCS on treatment. Lastly, the Kvale et al., (2020) study, with a large sample size (N = 163) showed no effect on treatment outcomes from DCS as compared to placebo controls.

With regards to D-Cycloserine's effects on insomnia, the findings are limited, but indicative. The first study showcasing the psychiatric effects of DCS reported the most pronounced effect on patients suffering from insomnia with the report stating: "such patients no longer experienced difficulty in falling asleep; they awakened well rested and with a general feeling of relaxation" (Crane, 1961, p. 54). In a RCT study looking at PTSD-treatment augmented with DCS, a significant improvement in sleep functioning was found, which increased over time at follow-up (Difede et al., 2014). This was measured as part of the PTSD-assessment and the authors highlighted the need for more specific sleep-assessment in DCS research. These preliminary findings are to the best of our knowledge the only experimental research on insomnia and DCS. Others have pointed out further theoretical

rationale for using DCS for insomnia treatment. They discussed an evolutionary model of sleep, wherein sleep difficulties can be seen as adaptive fear responses from our earlier history in unsafe environments, upheld as an evolutionary mismatch in safer modern surroundings (Perogamvros et al., 2020). The authors then suggested fear extinction therapy as most relevant for insomnia conditions, facilitated by DCS.

In light of the literature presented, we present a RCT study with difficult to treat OCD receiving the B4DT. Two groups received 100 mg and 250 mg of DCS respectively, controlled against a placebo group. Assessments were made at pre-treatment, post-treatment, 3-month and 12-month follow-up. The primary outcome measure was the Bergen Insomnia scale. We first hypothesized that B4DT would improve insomnia symptoms as measured by the BIS. Secondly, the study explored whether there are differences in the insomnia symptom reduction in the groups receiving DCS relative to the participants in the placebo group. Lastly, we investigated whether clinically significant insomnia would impair the treatment of OCD or impact the treatment's effect on depressive symptoms.

Methods

Fifteen specialized adult OCD teams, established by Norwegian health authorities across the country, participated in the study, with nine of these teams' recruiting participants. Management, data collection, therapist training, and treatment organization were centralized at the Bergen site **(**Kvale et al., 2018 & Launes et al., 2019 offer detailed information on the clinical training process**).** The study involved eight group leaders and 64 therapists. The study received approval from regional committees for medical and health research in Norway (reference number: 2013/195), and written consent was obtained from all participants.

Design and Procedures

Across four consecutive days, concentrated exposure and response prevention (ERP) treatment was administered to participants in groups of three to six patients, each with an assigned therapist. The second and third day were dedicated to exposure treatment. During the two exposure days, participants were given DCS, with dosages of either 100 mg and 250 mg or placebo due to the lack of clear optimal dosage guidelines (Mataix-Cols et al., 2019; Bürkner et al., 2017). The study employed a 3-group, placebo-controlled, triple-masked design, stratifying participants based on antidepressant use, due to findings of impairment on treatment response (Andersson et al., 2015). Randomization occurred within each stratum, assigning 100 mg, 250 mg DCS, or placebo in a 2:2:1 ratio among a sample of 163 patients. Randomization, performed in blocks of five via an online tool, remained concealed from independent assessors, therapists, and patients. The distribution among groups was as follows: 67 (41.1%) in the 250 mg group, 65 (39.9%) in the 100 mg group, and 31 (19.0%) in the placebo group. The study's announcement was facilitated through the Norwegian OCD association's and OCD teams' websites, along with diverse media outlets. Recruitment spanned from January 2016 to August 2017.

Patients included in the study met criteria for OCD according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, 2022). For inclusion, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) were used for screening. All patients who received a preliminary OCD diagnosis according to the MINI, also had a SCID-5 diagnostic interview (First et al., 2015). These interviews were conducted by trained independent assessors. Also, 20% of the taped interviews were rated by a second assessor.

Diagnostic agreement was high with an obtained kappa coefficient of 0.92. Y-BOCS interviews underwent the same procedure with a high interrater reliability of total score with an intraclass correlation coefficient of 0.94.

Included patients were adult outpatients, fluent in Norwegian, who had not responded to ERP treatment earlier or had experienced a relapse after responding to ERP treatment. The definition of responding to ERP was minimum 35% reduction with a post-treatment Y-BOCS score of maximum 15. The definition of relapse was minimum 35% increase from post-treatment Y-BOCS score; a Y-BOCS score of 16 ≥, in addition to a Clinical Global Impression (CGI) improvement score of 6 ≥ (i.e. "much worse"). The definition of non-responders was less than 35% reduction in OCD symptoms and a Y-BOCS score of 16 or more. To be able to participate, a minimum of 4 weeks since the end of last treatment was needed (Kvaale et al., 2020).

Patients with the following were excluded: ongoing substance abuse with or without dependence; psychosis or bipolar disorder; active suicidal ideation or plans; not receiving a stable dosage of antidepressants for at least 12 weeks or unwilling to receive a stable dosage during the four consecutive intervention days; not willing to abstain from anxiety-reducing substances during the exposure; intellectual disability; or had to travel more than one hour by train or car. Related to the DCS exclusion criteria were the following: pregnancy or breastfeeding, kidney impairment, porphyria, hypersensitivity to DCS and epilepsy.

Participants

Table 1 shows a summary of the pre-treatment characteristics of the sample. The mean age was 35 years and 72% were female. A total of 71% qualified for self-reported insomnia, while only 12% was diagnosed with insomnia or hypersomnia**.** The mean age of OCD onset was 19 years old, and the mean duration for OCD was 16 years. Following their last treatment, 62% were defined as having relapsed, while 38% were non-responders. There were no significant differences between the three groups apart from previous pre-treatment Y-BOCS scores, where the 250 mg group's mean score was lower than the two other groups.

Table 1

Pre-treatment Characteristics of the Sample (M(SD)/ %)

Characteristics	Total	250 mg	100 mg	Placebo
Insomnia				
BIS, self-reported	70.8%	63.9%	75.0%	75.9%
Insomnia, diagnosed	8.6%	5.8%	6.2%	19.4%
Hypersomnia, diagnosed	4.3%	4.5%	3.1%	6.5%
Insomnia/hypersomnia	12.0%	9.0%	9.2%	25.8%
Demographics				
Age	34.60 (10.87)	34.82 (11.75)	35.38 (11.42)	32.42 (7.06)
Female gender	71.8%	67.2%	75.4%	74.2%
OCD onset years	18.70 (9.92)	19.21 (10.29)	19.12 (10.70)	16.79 (7.22)
OCD duration years	16.17 (10.17)	15.89 (9.56)	16.58 (10.87)	15.93 (10.26)
OCD in family	42.1%	41.3%	41.9%	44.4%
Employment				
Work	34.4%	33.3%	38.5%	30.0%
Student	20.2%	27.3%	12.3%	23.3%
Disability	44.2%	39.4%	49.2%	46.7%
Single	47.5%	48.5%	43.1%	55.2%
Comorbid disorder	69.3%	68.7%	72.3%	64.5%
Psychotropic medication	46.6%	37.3%	55.4%	48.4%
SSRIs	31.9%	32.8%	33.8%	25.8%
Last treatment				
Y-BOCS pre	26.83 (5.00)	25.61 (4.79)	27.69 (4.99)	27.61 (5.07)
Y-BOCS post	14.14 (6.05)	14.51 (6.63)	13.52 (5.48)	14.69 (5.98)
Non-responder	38.7%	43.3%	35.4%	35.5%
Relapse	61.3%	56.7%	64.6%	64.5%
Current treatment				
Y-BOCS pre	25.16 (4.13)	24.68 (3.93)	25.52 (4.15)	25.42 (4.54)
PHQ-9 pre	11.96 (5.92)	11.40 (6.21)	12.75 (6.18)	11.43 (4.51)

Note. BIS, Bergen Insomnia Scale; OCD, Obsessive Compulsive Disorder; SSRIs, Selective Serotonin Reuptake Inhibitors; Y-BOCS, Yale-Brown Obsessive Compulsive Scale, PHQ-9, Personal Health Questionnaire-9; Pre, pre-treatment; Post, post-treatment.

Adherence and Competence

Video recordings were made for each group session and therapist meeting. Trained therapists, serving as observers and evaluators, ensured protocol adherence during all group sessions. Notably, no instances of protocol deviation were reported across any of the groups. Additionally, independent concentrated ERP experts, who did not partake in the sessions, assessed video recordings for both adherence and competency using a 3-point scale. The evaluation revealed that the vast majority of treatment groups, with the exception of one, exhibited good adherence and competence.

D-Cycloserine

On each of the two days of exposure it was administered one capsule of DCS with the respective 100 mg or 250 mg or one capsule of placebo. Both the DCS and placebo came in identical capsules produced by a research pharmacy. A letter containing information about DCS accompanied with a telephone number to address questions or to report adverse events. In some cases, when the exposure is short and does not result in a reduction in anxiety, there have been indications that DCS might potentiate negative experiences (Hofmann, 2014). In order to reduce the risk of this happening, the capsule was not taken before lunchtime on the second day, when the patient was familiar with the procedure. Assessors were questioned post-treatment to guess which dosage of medication the participants had obtained, and provide an estimation of how certain they were. There was no correspondence between the actual group and guesses made by the assessors ($x^2_4 = 2.62$; $p = .62$). Certainty was rated on a scale from 0 to 10 with a mean score of 4.0 and a standard deviation of 3.0. All patients completed the same questionnaire, with the same results in the form of no correspondence between the actual group and their guessing ($x^2_4 = 2.45$; $p = .65$). Patients' certainty had a mean of 0.3 with a standard deviation of 0.9.

Measures

The Bergen Insomnia Scale (BIS; Pallesen et al., 2008) was the primary outcome measure. The scale is based on the clinical criteria for insomnia outlined in the DSM-IV-TR. The first three items: difficulties with sleep onset, maintenance, and early morning wakening; correspond with criteria A (nocturnal symptoms) in DSM-IV, regarding difficulty initiating and maintaining sleep through the night. The last three items: not feeling adequately rested; experiencing daytime impairment, and feeling dissatisfied with sleep; correspond with criteria B. These two groups of items have been found to factor together in a clinical sample (Pallesen et al., 2008). The range of the total score of BIS goes from 0 to 42, where a greater score indicates more symptoms of insomnia. To qualify as clinically significant, one must score 3 or more on one of the items from 1-4 and 3 or more on item 5 or 6. The scale has shown good psychometric properties (Pallesen et al., 2008). Cronbach's alpha for the total score was .82.

The *Yale-Brown Obsessive-Compulsive Scale* (Y-BOCS; Goodman et al., 1989a) is a clinical interview used to assess severity of obsessive-compulsive symptoms. It consists of

five items that measure obsessive symptoms on a Likert-scale from 0 (no symptoms) to 4 (severe symptoms), and likewise five items that measure compulsive symptoms from 0 to 4. The Y-BOCS total score is the sum of the ten items with a range from 0 to 40. A higher score indicates more severe symptoms of OCD. Y-BOCS has documented solid psychometric qualities (Goodman et al., 1989a; 1989b; Abramowitz et al., 2010). Cronbach's alpha for the total score was .73.

The Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) is a self-report questionnaire consisting of nine items related to diagnosing depression in DSM-IV. PHQ-9 measures symptoms during the last two weeks on a Likert-scale from 0 (not at all) to 3 (almost every day). The total score ranges from 0 to 27, where a score from 5 to 9 is categorized as mild depressive symptoms; 10-14 as moderate; 15-19 as moderately severe and > 19 as severe (Kroenke et al., 2001). Cronbach's alpha for the total score was .86

Statistical Analysis

In order to investigate the effect across time in self-reported insomnia (i.e., the effect of B4DT) and whether there were differences in self-reported insomnia between the treatment conditions, a repeated split plot ANOVA was conducted. BIS was the dependent variable and condition (i.e. 250 mg, 100 mg and placebo) was the grouping variable. A repeated split plot ANOVA with the dependent variables Y-BOCS and PHQ-9 was also used to examine the general effect of B4DT on symptoms of OCD and depression. Effect sizes were calculated with pooled standard deviations.

To test if insomnia moderated treatment outcome, changes in Y-BOCS, BIS, and PHQ-9 were separately compared over time (pre-treatment, post-treatment, 3-month follow-up and 12-month follow-up) for patients who according to BIS qualified for insomnia vs. patients who did not. A repeated split plot ANOVA was also used for this purpose. The same procedure was also conducted for patients with no diagnosed insomnia vs. patients with diagnosed insomnia (n = 14) and hypersomnia (n = 7), which were merged together to one variable (n = 20, where one person was diagnosed with both conditions).

Missing items were imputed using the Expectation-Maximization method; 6.4% missing values for BIS. Data was missing completely at random, $x^2 = 257.42$, $df = 278$, $p = .81$. Missing values were not replaced if patients had missing values for all items of a measure (n = 9), hence the total sample size was 154.

Results

At 1-year follow-up, the total Y-BOCS score for all three conditions was significantly reduced with a large effect size of $d = 2.17$. The total PHQ-9 score for all three conditions was also significantly reduced with a small to moderate effect size $d = 0.41$. Symptoms of insomnia were also significantly reduced at 1-year follow-up with a small effect size $d = 0.23$. There was no significant interaction effect between time and condition on self-reported insomnia ($p = .87$), thus DCS did not augment treatment. A summary of changes in symptoms of insomnia, OCD, and depression is shown in Table 2.

Table 2

Changes in Insomnia, Symptoms of OCD, and Depression

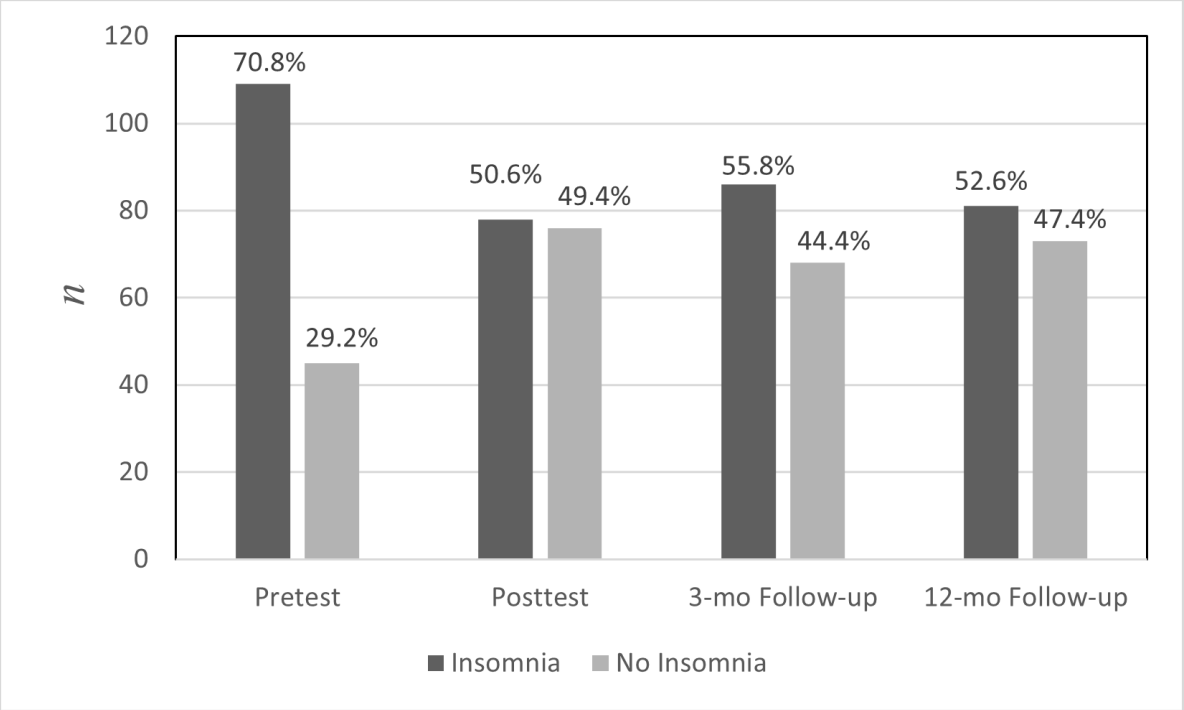
Measure	Pre	Post	3m FU	12m FU	*F*	*p*	*12m d*	time * group *p*
BIS								
250mg	16.15 (8.28)	12.92 (10.60)	12.23 (8.59)	13.85 (9.69)			0.26	
100mg	19.45 (10.62)	14.97 (10.60)	15.29 (10.43)	16.65 (10.98)			0.26	
Placebo	18.27 (9.71)	15.07 (11.92)	16.00 (9.48)	17.12 (10.78)			0.11	
Total	17.92 (9.64)	14.17 (10.84)	14.21 (9.64)	15.63 (10.48)	12.70	<.001	0.23	.87
Y-BOCS								
250mg	26.60 (4.04)	11.75 (5.44)	13.23 (7.58)	14.63 (7.38)			2.01	
100 mg	27.24 (3.67)	11.78 (5.75)	13.25 (6.63)	14.19 (7.09)			2.31	
Placebo	27.20 (3.83)	14.27 (7.16)	16.10 (7.23)	14.30 (7.62)			2.14	
Total	26.98 (3.83)	12.28 (6.00)	13.83 (7.18)	14.38 (7.26)	246.16	<.001	2.17	.28
PHQ-9								
250mg	11.47 (6.04)	7.12 (6.02)	6.54 (5.55)	8.61 (5.93)			0.48	
100 mg	12.77 (5.90)	8.78 (6.12)	9.17 (6.29)	10.27 (6.32)			0.41	
Placebo	11.44 (5.70)	7.60 (5.56)	8.48 (4.21)	10.00 (6.07)			0.24	
Total	12.01 (5.70)	7.91 (6.01)	7.99 (5.77)	9.56 (6.13)	33.73	<.001	0.41	.63

Note. BIS, Bergen Insomnia Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PHQ-9, Patient Health Questionnaire-9. Pre, pre-treatment; Post, post-treatment; 3m FU, 3-month follow-up; 12m FU, 12-month follow-up. $N = 163$

Before treatment there were 109 patients (70%) with self-reported insomnia (total N = 154). After one year it was reduced with 26% to 81 (52%) (see Figure 1), with an effect size of d = 0.36.

Figure 1

Changes in Self-reported Clinical Insomnia (BIS)



Note. Clinical Insomnia measure according to BIS, Bergen Insomnia Scale; 3-mo Follow-up, 3-months follow-up; 12-mo Follow-up, 12-month follow-up; N = 154.

There was no significant interaction effect between self-reported insomnia and changes in symptoms of OCD or depression (see Table 3). Similar results were obtained for patients with diagnosed insomnia/hypersomnia as there was no significant group*time interaction on Y-BOCS (p = .49), PHQ-9 (p = .95), or BIS (p = .31). However, there was a significant interaction effect between self-reported insomnia and changes in BIS-scores across time (p = .02). Patients with self-reported insomnia had a reduction in insomnia symptoms, while patients without insomnia showed no change.

Table 3

Test of Moderation Effects of Self-Reported Insomnia (BIS) on Treatment Outcome

Measure	Pre	Post	3m FU	12m FU			*12m*	time * group
	M (SD)				*F*	*p*	*d*	*p*
BIS								
Insomnia	22.26 (7.63)	17.80 (10.52)	17.34 (9.33)	19.05 (10.16)			0.36	
No insomnia	7.41 (4.50)	5.40 (5.04)	6.64 (5.14)	7.34 (5.42)			0.01	
Total	17.92 (9.64)	14.17 (10.84)	14.21 (9.64)	15.63 (10.48)	9.21	<.001	0.23	.02
Y-BOCS								
Insomnia	27.17 (3.20)	12.32 (5.92)	13.52 (6.94)	14.67 (6.88)			2.33	
No Insomnia	26.53 (3.20)	11.63 (5.88)	14.25 (7.57)	14.00 (6.88)			2.34	
Total	26.99 (3.75)	12.12 (5.89)	13.73 (7.11)	14.48 (7.27)	222.24	<.001	2.16	.61
PHQ-9								
Insomnia	13.46 (5.59)	8.74 (6.30)	9.12 (5.96)	11.01 (6.18)			0.42	
No Insomnia	8.49 (3.99)	5.46 (4.11)	5.20 (4.03)	6.07 (4.13)			0.60	
Total	12.00 (5.64)	7.78 (5.92)	7.97 (5.74)	9.56 (6.08)	30.89	<.001	0.42	.19

Note. BIS, Bergen Insomnia Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PHQ-9, Patient Health Questionnaire-9; Pre, Pre-treatment; Post, Post-treatment; 3m FU, 3-month follow-up; 12m FU, 12-months follow-up. $N = 154$.

Discussion

This study aimed to investigate the effects of concentrated exposure and response prevention treatment on insomnia symptoms, explore the potential augmentation by DCS, and examine how clinical insomnia might moderate the treatment effect. A significant effect of the B4DT on insomnia symptoms was found. No difference between the groups was discovered, showing no augmentation from DCS. Furthermore, clinically insomnia did not moderate OCD-treatment outcomes.

The first hypothesis was confirmed, adding to the small, but growing literature on the effects on concomitant insomnia for the B4DT specifically and CBT for anxiety disorders more generally. The effect size at 3-month follow-up in this study (d = 0.38) was slightly weaker compared to the moderate ones found (d = 0.55; 0.53) at 6-month and 3-month follow-up in earlier studies on the B4DT (Hagen et al., 2021; Nordahl et al., 2018) and even smaller (d = 0.23) at the 1-year follow-up. The smaller effect size could be attributed to the larger sample size in the present study and the sample comprising participants with difficult-to-treat OCD. Still, a robust effect was found and one possible mechanism behind this could be the bidirectional model concerning the relationship between OCD and insomnia (Cox et al., 2018). As the participants received concentrated exposure and response prevention treatment, they learned techniques to deal with their OCD, which in turn may lessen the rumination and negative activation often found in insomnia. Then the higher sleep quality could increase cognitive control, further strengthening the response prevention and OCD-symptom reduction (Timpano et al., 2014). This effect of the B4DT on concomitant sleep difficulties might further bolster the OCD-symptom reduction over time.

It is worth noting that the greatest effect on insomnia symptoms was found from pre- to post-treatment (d = 0.37) and from pre- to 3-month follow-up (d = 0.38), with a smaller effect at 1-year follow-up (d = 0.23). This contrasts with the Hagen et al. (2021) study, where the opposite was observed. They attributed this to a longer onset of insomnia improvement following the B4DT. If the relationship between OCD and insomnia is bi-directional, one would expect the remission of OCD at post-treatment to give immediate reductions in insomnia, as the obsessive and compulsive thoughts no longer keep the patients activated and awake. In addition to the effect found on BIS scores, this effect corresponded to a substantial reduction of clinically indicated insomnia on the BIS, from 70% at pre-treatment to 52% at the 1-year follow-up.

The high prevalence of self-reported insomnia (70%) at pre-treatment added to the growing consensus in the literature of a consistent link between OCD and insomnia (Cox et al., 2020). However, as seen in the pre-treatment characteristics only 14 of the participants qualified for comorbid insomnia and 7 for hypersomnia as per the SCID-5, as opposed to the 109 with clinically indicated insomnia according to the BIS. A similar difference was found in the Nordahl et al. (2021) study, 81% with clinically indicated insomnia on the BIS opposed to 19% with comorbid insomnia on the clinical interview. This large discrepancy in both studies is interesting as both measures are based on the DSM diagnostic criteria (the 4th version for BIS and the 5th for SCID-5). The authors of the BIS point out the main differences between their scale and the DSM-5 insomnia diagnosis, namely that the BIS does not differentiate between primary insomnia and insomnia explained by coexisting mental conditions (Pallesen et al., 2008).

While using the DSM-5 diagnostic criteria, insomnia explained by other mental illnesses should not be coded as comorbid insomnia (DSM-5, 2022). This means that sleep difficulties presumed by the assessor to be explained by OCD, would not get labeled as comorbid insomnia. This might entail that a large proportion of the insomnia is linked to the OCD while the ones diagnosed with comorbid insomnia were considered to have a more separate sleep condition. Another potential reason for the discrepancy is the items in the BIS which only correspond to the last month, while the DSM-V requires the presence of insomnia symptoms over a period of at least three months. As the discrepancy was present in two studies it might be something to consider for future revisions of the BIS, as the clinical cut-off scores could be seen as too low. For future research one could also consider employing physiological measures as a supplement.

The second hypothesis explored augmentation of DCS and showed no effect in comparison with the placebo group. This is in line with the newest review in the literature showing next to zero effect size on DCS (Bürkner et al., 2017). The authors pointed out that the newer, high-quality studies report smaller or no-effects of DCS on anxiety disorders. Thus, the present study, with a large sample size and robust controls, could be expected to show a smaller or non-significant effect. Additionally, the Kvale et al. (2020) study, based on the same data as this study, found no effect on OCD-symptoms between the groups. If there exists a bi-directional relationship between OCD and insomnia, no differential effect on OCD might warrant no effect of DCS on insomnia. As mentioned, there exists only one controlled

study looking at the effects of DCS on sleep, and they only studied it as part of the PTSD assessment (Difede et al., 2014). They found a significant effect but highlighted the need for specific sleep assessment and larger samples. As this study on OCD found no effect, improvement of insomnia symptoms augmented by DCS seems less likely to be a promising route.

We found non-significant differences in OCD outcome as measured by the Y-BOCS between the group with clinical indications of insomnia and the one without. The same was found for depressive symptoms as measured by the PHQ-9. Likewise we found non-significant differences between the group with diagnosed comorbid insomnia and the one without. This is in accordance with other studies showing no impairment of insomnia on OCD treatment (Hagen et al., 2021; Nordahl et al., 2018). This implicates that insomnia should not be considered an exclusion criterion for OCD-treatment, nor as impairing the treatment. This is in contrast to an earlier review by Cox et al. (2018) showing that sleep disturbance did limit OCD treatment response in some samples. Why the results are different in these newer studies is unclear, but one reason why sleep difficulties did not impair treatment might be the intensive format of the B4DT. It could still be an issue in more traditional long-term treatment.

There are some important limitations of this study that should be considered. Firstly, the sleep assessment employed for the three hypotheses, while psychometrically well tested, is still only a subjective, self-report measure of insomnia symptoms. It can only give indications about clinical insomnia, while the full clinical interview found a different prevalence of clinical insomnia in the sample. Furthermore, objective metrics, such as measures of circadian rhythms and sleep effectiveness would provide a more complete picture of the participants' sleep quality (Nota et al., 2015). The RCT-design and large sample size make the testing of DCS augmentation robust, but the effects of the treatment itself are not controlled in this study. Comparing a treatment group to a control group would increase the robustness of the results. For this wait list or no-care controls are often employed, but the newest Cochrane review of control interventions suggests that usual-care controls give more reliable results (Faltinsen et al., 2023). This is like the control groups used in the Hagen et al. (2021) study, with findings akin to ours, only a larger effect size.

The sample had a clear skewness in gender, composed mostly of women (71%). A certain skewness is to be expected however, as the prevalence of OCD worldwide is larger

among women (1.5%) than men (1.0 %) (Fawcett et al., 2020). Lastly one could also consider whether the dosing procedure chosen for this study is optimal. A recent review of the DCS literature relates the decline in effect in DCS research to suboptimal dosing regimens (Rosenfield et al., 2019). They investigated most studies on DCS and showed how the studies who administer more doses (up to 9) and 60 minutes prior to treatment had the largest effect. While something to consider for future research, it would not be feasible in the present study due to the concentrated treatment over two sessions of exposure. Treatment with more exposure sessions and thus DCS doses might see an effect. Alternatively, as patients are supposed to keep up the exposure on their own, one could try giving them DCS for their own exposure sessions following the B4DT. This is somewhat risky however, as DCS can have adverse effects if anxiety is not reduced following the exposure (Hofmann, 2014).

The results of this study are promising regarding improving concomitant insomnia with OCD-treatment, while showing less promise in augmenting this treatment with DCS. Future research should focus on doing controlled studies specifically targeting insomnia with more comprehensive measures of sleep difficulty, while considering different dosing procedures with DCS. While reduced, the symptom severity of sleep difficulties for this sample remains high. Testing specific treatment for their insomnia is prudent, with CBT-I treatment now recommended as first-line treatment for insomnia, with systematic reviews showing a strong effect size on the Insomnia Severity Index (ISI) (d = 0.98) at post-treatment and moderate (d = 0.64) at the 3-month follow-up (van Straten et al., 2018; van der Zweerde et al., 2019). This form of CBT is employed both individually and in group settings. It typically involves elements of sleep deprivation, stimulus control and sleep hygiene. This combined with the small to moderate effects CBT-treatment has on concomitant sleep difficulties seems a more promising path forward than DCS augmentation (Belleville et al., 2010). If the bi-directional model holds, this treatment might in turn bolster the OCD-treatment for this group. While this study adds to the link between OCD and insomnia, more longitudinal studies could also be considered to investigate their unique relationship. One possible route would be examining whether symptom severity of insomnia predicts OCD treatment outcome or vice-versa.

In conclusion, this randomized clinical trial found no potentiation of DCS for symptoms of insomnia following response prevention and concentrated exposure treatment for OCD. A weak improvement on insomnia symptoms following treatment were found for

all groups, strongest at post-treatment. Insomnia symptoms did not moderate treatment outcome. Future research should test the effect of specific insomnia treatment for patients with OCD and comorbid insomnia.

References

Abramowitz, J. S., Deacon, B. J., Olatunji, B. O., Wheaton, M. G., Berman, N. C., Losardo, D., Timpano, K. R., McGrath, P. B., Riemann, B. C., & Adams, T. (2010). Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the Dimensional Obsessive-Compulsive Scale. *Psychological assessment*, *22*(1), 180. https://doi.org/10.1037/a0018260

Andersson, E., Hedman, E., Enander, J., Radu Djurfeldt, D., Ljótsson, B., Cervenka, S., Isung, J., Svanborg, C., Mataix-Cols, D., Kaldo, V., Andersson, G., Lindefors, N., & Rück, C. (2015). d-Cycloserine vs Placebo as Adjunct to Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder and Interaction With Antidepressants: A Randomized Clinical Trial. *JAMA psychiatry*, *72*(7), 659-667. https://doi.org/10.1001/jamapsychiatry.2015.0546

Belleville, G., Cousineau, H., Levrier, K., St-Pierre-Delorme, M.-E., & Marchand, A. (2010). The impact of cognitive-behavior therapy for anxiety disorders on concomitant sleep disturbances: a meta-analysis. In *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*. Centre for Reviews and Dissemination (UK). https://dx.doi.org/10.1016/j.janxdis.2010.02.010

Bürkner, P.-C., Bittner, N., Holling, H., & Buhlmann, U. (2017). D-cycloserine augmentation of behavior therapy for anxiety and obsessive-compulsive disorders: A meta-analysis. *PloS one*, *12*(3), e0173660. https://doi.org/10.1371/journal.pone.0173660

Cox, R. C., Jessup, S., & Olatunji, B. O. (2018). Sleep disturbance in obsessive-compulsive disorder: Preliminary evidence for a mechanistic relationship. *Current Sleep Medicine Reports*, *4*, 89-93. https://doi.org/10.1007/s40675-018-0109-4

Cox, R. C., Parmar, A. M., & Olatunji, B. O. (2020). Sleep in obsessive-compulsive and related disorders: a selective review and synthesis. *Current Opinion in Psychology*, *34*, 23-26. https://doi.org/10.1016/j.copsyc.2019.08.018

Crane, G. E. (1961). The psychotropic effects of cycloserine: a new use for an antibiotic. *Comprehensive Psychiatry*, *2*(1), 51-59. https://doi.org/10.1016/S0010-440X(61)80007-2

Difede, J., Cukor, J., Wyka, K., Olden, M., Hoffman, H., Lee, F. S., & Altemus, M. (2014). D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. *Neuropsychopharmacology*, *39*(5), 1052-1058. https://doi.org/10.1038/npp.2013.317

Faltinsen, E., Todorovac, A., Bruun, L. S., Hróbjartsson, A., Gluud, C., Kongerslev, M. T., Simonsen, E., & Storebø, O. J. (2023). Control interventions in randomised trials among people with mental health disorders: a Cochrane Review. *BJPsych Advances*, *29*(4), 224-224. https://doi.org/10.1192/bja.2023.25

Fawcett, E. J., Power, H., & Fawcett, J. M. (2020). Women are at greater risk of OCD than men: a meta-analytic review of OCD prevalence worldwide. *The Journal of clinical psychiatry*, *81*(4), 13075. https://doi.org/10.4088/JCP.19r13085

First, M., Williams, J., Karg, R., & Spitzer, R. Structured clinical interview for DSM-5—research version; 2015. *Arlington, VA, American Psychiatric Association*. https://doi.org/10.1002/9781118625392.wbecp351

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The yale-brown obsessive compulsive scale: II. Validity. *Archives of general psychiatry*, *46*(11), 1012-1016. https://doi.org/10.1001/archpsyc.1989.01810110054008

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. *Archives of general psychiatry*, *46*(11), 1006-1011. https://doi.org/10.1001/archpsyc.1989.01810110048007

Hagen, K., Nordahl, H., Launes, G., Kvale, G., Öst, L.-G., Hystad, S., Hansen, B., & Solem, S. (2021). Does concentrated exposure treatment for obsessive-compulsive disorder improve insomnia symptoms? results from a randomized controlled trial. *Frontiers in Psychiatry*, *12*, 625631. https://doi.org/10.3389/fpsyt.2021.625631

Hansen, B., Hagen, K., Öst, L.-G., Solem, S., & Kvale, G. (2018). The Bergen 4-day OCD treatment delivered in a group setting: 12-month follow-up. *Frontiers in psychology*, 639. https://doi.org/10.3389/fpsyg.2018.00639

Hansen, B., Kvale, G., Hagen, K., Havnen, A., & Öst, L.-G. (2019). The Bergen 4-day treatment for OCD: four years follow-up of concentrated ERP in a clinical mental health setting. *Cognitive Behaviour Therapy*, *48*(2), 89-105. https://doi.org/10.1080/16506073.2018.1478447

Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011). Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms. *Clinical Psychology Review*, *31*(2), 225-235. https://doi.org/10.1016/j.cpr.2010.04.003

Hofmann, S. G. (2014). D-cycloserine for treating anxiety disorders: making good exposures better and bad exposures worse. *Depression and anxiety*, *31*(3), 175. https://doi.org/10.1002/da.22257

Koffel, E. A., Koffel, J. B., & Gehrman, P. R. (2015). A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep Medicine Reviews*, *19*, 6-16. https://doi.org/10.1016/j.smrv.2014.05.001

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine*, *16*(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Kvale, G., Hansen, B., Björgvinsson, T., Børtveit, T., Hagen, K., Haseth, S., Kristensen, U. B., Launes, G., Ressler, K. J., & Solem, S. (2018). Successfully treating 90 patients with obsessive compulsive disorder in eight days: the Bergen 4-day treatment. *BMC psychiatry*, *18*, 1-9. https://doi.org/10.1186/s12888-018-1887-4

Launes, G., Laukvik, I. L., Sunde, T., Klovning, I., Hagen, K., Solem, S., Öst, L.-G., Hansen, B., & Kvale, G. (2019). The Bergen 4-day treatment for obsessive-compulsive disorder: does it work in a new clinical setting? *Frontiers in psychology*, *10*, 1069. https://doi.org/10.3389/fpsyg.2019.01069

Mataix-Cols, D., De La Cruz, L. F., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., Frumento, P., De Kleine, R. A., Difede, J., & Dunlop, B. W. (2017). D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: a systematic review and meta-analysis of individual participant data. *JAMA psychiatry*, *74*(5), 501-510. https://doi.org/10.1001/jamapsychiatry.2016.3955

Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological psychiatry*, *63*(12), 1118-1126. https://doi.org/10.1016/j.biopsych.2008.01.012

Nordahl, H., Havnen, A., Hansen, B., Öst, L. G., & Kvale, G. (2018). Sleep disturbances in treatment-seeking OCD-patients: Changes after concentrated exposure treatment. *Scandinavian journal of psychology*, *59*(2), 186-191. https://doi.org/10.1111/sjop.12417

Nota, J. A., Sharkey, K. M., & Coles, M. E. (2015). Sleep, arousal, and circadian rhythms in adults with obsessive–compulsive disorder: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *51*, 100-107. https://doi.org/10.1016/j.neubiorev.2015.01.002

Palagini, L., Hertenstein, E., Riemann, D., & Nissen, C. (2022). Sleep, insomnia and mental health. *Journal of Sleep Research*, *31*(4), e13628. https://doi.org/10.1111/jsr.13628

Pallesen, S., Bjorvatn, B., Nordhus, I. H., Sivertsen, B., Hjørnevik, M., & Morin, C. M. (2008). A new scale for measuring insomnia: the Bergen Insomnia Scale. *Perceptual and motor skills*, *107*(3), 691-706. https://doi.org/10.2466/pms.107.3.691-706

Perogamvros, L., Castelnovo, A., Samson, D., & Dang-Vu, T. T. (2020). Failure of fear extinction in insomnia: an evolutionary perspective. *Sleep Medicine Reviews*, *51*, 101277. https://doi.org/10.1016/j.smrv.2020.101277

Ramsawh, H. J., Bomyea, J., Stein, M. B., Cissell, S. H., & Lang, A. J. (2016). Sleep quality improvement during cognitive behavioral therapy for anxiety disorders. *Behavioral Sleep Medicine*, *14*(3), 267-278. https://doi.org/10.1080/15402002.2014.981819

Reynolds, S. A., & Ebben, M. R. (2017). The cost of insomnia and the benefit of increased access to evidence-based treatment: cognitive behavioral therapy for insomnia. *Sleep medicine clinics*, *12*(1), 39-46. https://doi.org/10.1016/j.jsmc.2016.10.011

Riemann, D., Benz, F., Dressle, R. J., Espie, C. A., Johann, A. F., Blanken, T. F., Leerssen, J., Wassing, R., Henry, A. L., & Kyle, S. D. (2022). Insomnia disorder: State of the science and challenges for the future. *Journal of Sleep Research*, *31*(4), e13604. https://doi.org/10.1111/jsr.13604

Rosenfield, D., Smits, J. A., Hofmann, S. G., Mataix-Cols, D., de la Cruz, L. F., Andersson, E., Rück, C., Monzani, B., Pérez-Vigil, A., & Frumento, P. (2019). Changes in dosing and dose timing of D-cycloserine explain its apparent declining efficacy for augmenting exposure therapy for anxiety-related disorders: an individual participant-data meta-analysis. *Journal of anxiety disorders*, *68*, 102149. https://doi.org/10.1016/j.janxdis.2019.102149

Schade, S., & Paulus, W. (2016). D-cycloserine in neuropsychiatric diseases: a systematic review. *International Journal of Neuropsychopharmacology*, *19*(4), pyv102. https://doi.org/10.1093/ijnp/pyv102

Sevilla-Cermeño, L., Isomura, K., Larsson, H., Åkerstedt, T., Vilaplana-Pérez, A., Lahera, G., Mataix-Cols, D., & de la Cruz, L. F. (2020). Insomnia in obsessive-compulsive disorder: a Swedish population-based cohort study. *Journal of Affective Disorders*, *266*, 413-416. https://doi.org/10.1016/j.jad.2020.01.122

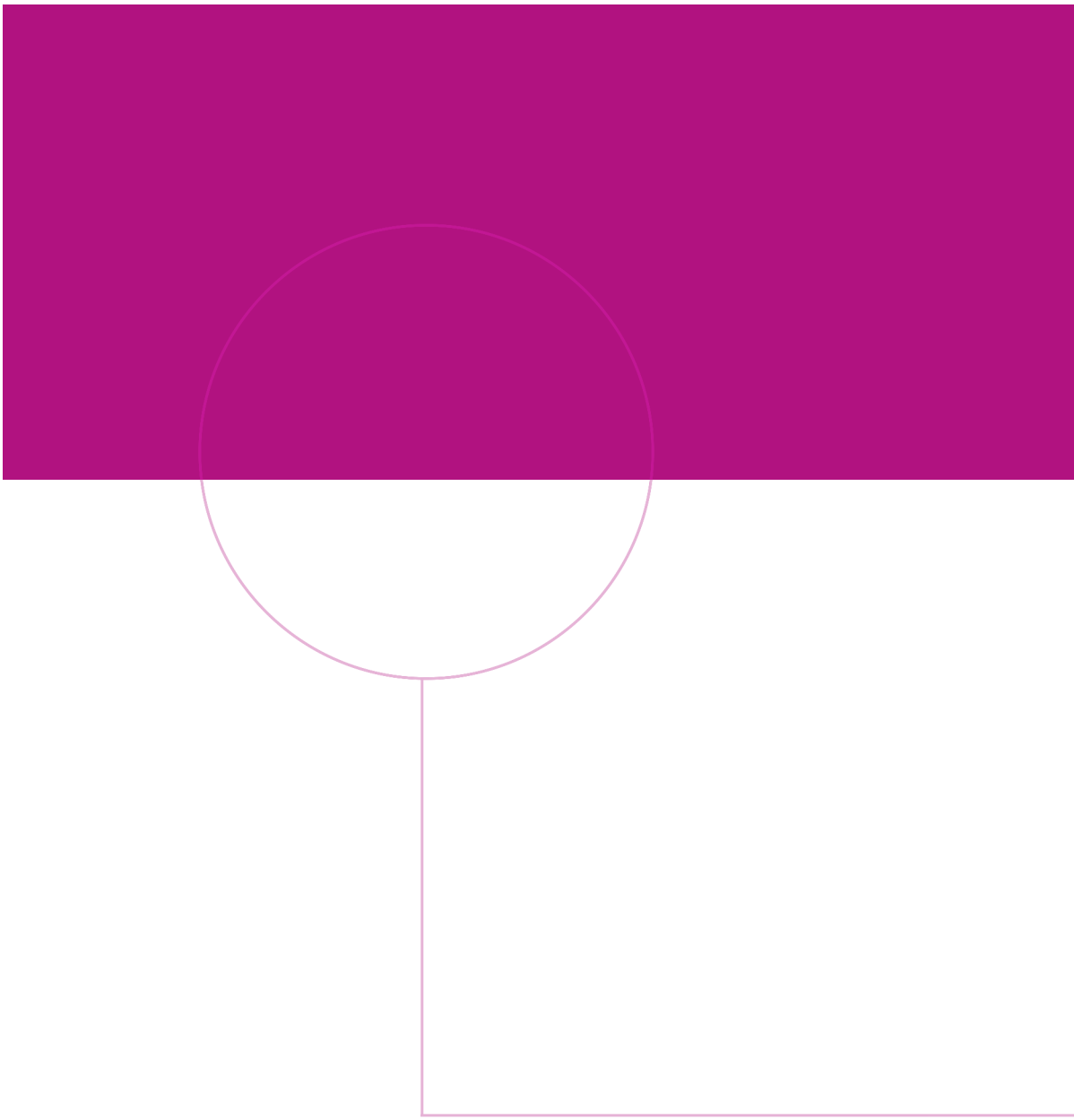
Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of clinical psychiatry*, *59*(20), 22-33.

Timpano, K. R., Carbonella, J. Y., Bernert, R. A., & Schmidt, N. B. (2014). Obsessive compulsive symptoms and sleep difficulties: exploring the unique relationship between insomnia and obsessions. *Journal of psychiatric research*, *57*, 101-107. https://doi.org/10.1016/j.jpsychires.2014.06.021

Trauer, J. M., Qian, M. Y., Doyle, J. S., Rajaratnam, S. M., & Cunnington, D. (2015). Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Annals of internal medicine*, *163*(3), 191-204. https://doi.org/10.7326/M14-2841

van der Zweerde, T., Bisdounis, L., Kyle, S. D., Lancee, J., & van Straten, A. (2019). Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. *Sleep medicine reviews*, *48*, 101208. https://doi.org/10.1016/j.smrv.2019.08.002

Van Straten, A., van der Zweerde, T., Kleiboer, A., Cuijpers, P., Morin, C. M., & Lancee, J. (2018). Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. *Sleep medicine reviews*, *38*, 3-16. https://doi.org/10.1016/j.smrv.2017.02.001



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