Antidepressant use with D-Cycloserine may block fear extinction

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ABSTRACT FROM: Andersson E, Hedman E, Enander J, *et al*. D-Cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: a randomized clinical trial. *JAMA Psychiatry* 2015;72:659–67.

WHAT IS ALREADY KNOWN ON THIS TOPIC

D-Cycloserine (DCS) is a partial agonist at the *N*-methyl-d-aspartate receptor, which facilitates extinction learning in animal models and augments exposure therapy in humans with anxiety disorders and obsessive-compulsive disorder (OCD).[1] In OCD, there have been other small randomised, placebo-controlled trials, in children and adults, examining DCS augmentation of exposure therapy, with inconsistent findings as to whether DCS is superior to placebo at post-treatment or follow-up.[2–4] This study, which examined the efficacy of DCS augmentation of a validated internet-based cognitive–behavioural therapy (ICBT) for OCD, is the first large-scale trial on DCS augmentation of CBT for OCD, and contributes to a growing body of literature on the moderators of DCS efficacy, suggesting that DCS is not universally effective.

METHODS OF THE STUDY

Andersson and colleagues examined 128 adult outpatients with a primary diagnosis of OCD and an Yale-Brown Obsessive-Compulsive Scale (YBOCS) score of 16 or higher, representing the largest sample of individuals with OCD in a published DCS trial to date. Participants were unmedicated or taking antidepressant medication for at least 2 months at a stable dose prior to enrolment and were willing to stay on the same dose during the trial. All participants received 12 weeks of ICBT and were randomly assigned to receive 50 mg of DCS or placebo in addition to ICBT. DCS or placebo was self-administered 1 h prior to five exposure tasks. The study used a double-blinded design and experienced psychiatrists conducted assessments of the clinician-administered YBOCS at pretreatment, post-treatment and 3-month follow-up time points.

WHAT THIS PAPER ADDS

- Although the primary intent-to-treat analyses showed that both DCS and placebo groups improved with CBT (DCS did not enhance the benefits of CBT compared with placebo at post-treatment or 3-month follow-up), antidepressant use significantly impaired treatment response in the DCS group, but not the placebo group.
- This is the first study to date to directly examine the effect of concomitant antidepressants on DCS efficacy in humans. Past human trials have focused exclusively on the efficacy of DCS and rate of DCS-augmented treatment response. It addresses an important clinical question, as antidepressants are the most effective psychotropic medications for OCD.

LIMITATIONS

- These results are preliminary, as the moderating effect of antidepressants in this study is a post hoc finding. As such, participants were not randomised to receive antidepressants or not, and may not be matched on all aspects that could impact treatment response.
- The findings are limited to a self-selected sample of adults with OCD, who volunteered to participate in ICBT and therefore not generalisable to all patients with OCD.

WHAT NEXT IN RESEARCH

- DCS augmentation of CBT may only be beneficial under specific conditions. Future research will need to examine the optimal dose, dose timing (eg, before or after exposures)[5] and frequency of DCS administration, as these methodological factors may contribute to the inconsistent findings in the literature.
- Future studies should also continue to identify subgroups of individuals who may respond better to DCS than others (eg, being antidepressant naïve, etc).
- Given that the current study was conducted in Swedish and most ICBT protocols are tested in Europe and Australia, future research should also examine ICBT in the English language in the USA.

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

No. This study encourages us to refer patients to ICBT and to bring more ICBT interventions to the USA. Given that it is the first human trial to suggest that antidepressants may impair the effects of DCS and this was a post hoc finding, the results are too preliminary to change clinical practice. These results require replication in a large randomised controlled trial in which antidepressant use is randomised. In addition, the biological mechanisms underlying this result still need to be examined.

Competing interests SW has received research support in the form of free medication and matching placebo from Forest Laboratories for the current clinical trial. SW is a presenter for the Massachusetts General Hospital Psychiatry Academy in educational programmes supported through independent medical education grants from pharmaceutical companies; she has received royalties from Elsevier Publications, Guilford Publications and New Harbinger Publications from Oxford University Press. She has also received salary support from Novartis. SW has also received speaking honoraria from various academic institutions and foundations, including the International Obsessive Compulsive Disorder Foundation and the Tourette's Syndrome Association. In addition, she received payment from the Association for Behavioral and Cognitive Therapies for her role as Associate Editor for the Behavior Therapy journal, as well as from John Wiley & Sons, Inc. for her role as associate editor on the journal *Depression and Anxiety*.

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