

Results of D-Cycloserine Therapy for PTSD Prove Underwhelming

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MONTREAL – The addition of d-cycloserine to cognitive-behavioral therapy for the treatment of posttraumatic stress disorder showed little or no benefit over placebo, based on several studies presented at the annual meeting of the International Society for Traumatic Stress Studies.

The presentations sparked some heated debate and dampened hopes for the drug in treating posttraumatic stress disorder (PTSD), given that it has already shown promise in the treatment of social anxiety disorder, panic disorder, and some phobias – and might have potential in the treatment of obsessive-compulsive disorder and addictions.

"The early results are not as positive as we [had] hoped," commented Dr. Charles Marmar, professor and chair of the department of psychiatry at New York University, when asked to comment after the session. "We didn't see much evidence today that d-cycloserine boosts the therapeutic benefit of cognitive-behavioral therapy [CBT] in PTSD," agreed Dr. Roger Pitman, director of the Massachusetts General Hospital posttraumatic stress disorder and psychophysiology laboratory and professor of psychiatry at Harvard Medical School, both in Boston.

But Dr. Pitman cautioned against dismissing the potential of d-cycloserine (DCS) in psychiatry. "There are several published studies now in social phobia, panic disorder, and height phobia that you can't simply dismiss," he said in an interview. "It's fair to conclude that DCS has the capability of bolstering cognitive-behavioral therapy by enhancing retention, but maybe PTSD is a tougher nut to crack."

d-cycloserine, a broad-spectrum antibiotic that has been used for decades in the treatment of tuberculosis and urinary tract infections, also is known to be a cognitive enhancer. In animal laboratory work, DCS been shown to reduce fear in mice. Its positive effect in the treatment of human anxiety and phobia studies is believed to stem from the drug's ability to enhance learning of new responses to stressful stimuli.

"Maybe for PTSD, the neurobiological mechanisms that are associated with maintenance of this disorder are more complex than those associated with less complex disorders such as social anxiety," suggested Stéphane Guay, Ph.D., director of the trauma study center at Louis-H. Lafontaine Hospital in Montreal, who presented one of the negative DCS studies at the meeting, cosponsored by Boston University.

His randomized, double-blind placebo-controlled trial included 45 adult PTSD patients, with moderate to severe symptoms. All patients received 11 or 12 sessions (duration, 90 minutes) of CBT combined with either placebo (n = 23) or DCS (n = 22) 50 mg, administered 1 hour prior to the session for sessions 4 through 11.

The idea behind administration of the drug is that cognitive-behavioral therapy is based on learning, and DCS can enhance learning, he explained. CBT was manualized, and included psychoeducation about posttraumatic stress disorder, prolonged imaginal exposure, and breathing retraining.

The main outcomes were PTSD symptoms, measured with the Clinician-Administered PTSD Scale (CAPS) and the Structured Clinical Interview for DSM-IV Disorders (SCID), and depression, measured by the Beck Depression Inventory (BDI).

Remission rates were roughly equivalent in both groups at 55% for the placebo group and 48% for the treated group immediately following the treatment, and 59% and 44% at the 6-month follow-up. "We found that DCS didn't seem to improve or increase or accelerate the treatment," he said in an interview. "In fact, those who received DCS did worse in general."

The researchers analyzed a subgroup of patients who were depressed at baseline and found that while CAPS scores dropped for nondepressed patients, they remained almost the same in the depressed group. "These data do not support the use of DCS as an adjunct to CBT in PTSD and show a negative interaction between PTSD, major depression, and DCS," he concluded. "The mechanism of major depression and PTSD may be different."

Two other studies presented during the session had not yet been unblinded, so no reliable conclusions could be drawn, and a third study of 20 patients randomized to CBT plus placebo or CBT plus d-cycloserine showed little difference between groups except a slightly more rapid onset of improvement in the DCS group, reported Clare Henn-Haase, Psy.D., a research psychologist at the San Francisco VA Medical Center.

Asked to comment on the presentations, Rachel Yehuda, Ph.D., professor of psychiatry at Mount Sinai School of Medicine and director of mental health at the James J. Peters VA Medical Center, both in New York, expressed concern that there was too much unfounded optimism in the face of the underwhelming findings.

"I am challenging my clinical colleagues to not get too excited because the basic scientists are staying more sober," she said, referring to the earlier session that presented findings of this therapy in mice.

"They're not presenting the negatives of the data with adequate emphasis – it's as simple as that," added Dr. Alexander McFarlane, director of the Centre for Military and Veterans' Health and professor of psychiatry at the University of Adelaide (Australia). "You can see there's a real desire to bring the world of psychotherapy and the world of pharmacology together. There's tremendous investment in this idea. The trouble is, you always have inconvenient truths, and it's about not running away from them. Good science is to face those inconsistencies."

But Dr. Pitman was more optimistic. "The goal of DCS is to facilitate the consolidation of extinction learning. It's called extinction retention. We've published data that extinction retention is deficient in posttraumatic stress disorder, so the idea that extinction retention could be boosted by an agent like DCS is very attractive," he said.

The field is still very new, and gaps in knowledge are numerous, both at the basic science and clinical level, said Dr. Marmar, urging patience.

"The fact that DCS has been shown to accelerate or improve the effectiveness of behavioral treatments for other disorders, like phobia, social anxiety, and some others suggests we should continue to work on this drug with PTSD – and try to refine it and try to determine the optimal parameters in dosing and scheduling."

None of the presenters reported having conflicts of interest.

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