D-Cycloserine for PTSD Proves Underwhelming

BY KATE JOHNSON

FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR TRAUMATIC STRESS STUDIES

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 meeting.

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, who serves as 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.

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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.

VITALS

Major Finding: Remission rates were at 55% for the placebo group and 48% for the treated group immediately after the treatment.

Data Source: Several studies testing the effects of D-cycloserine given a few hours before cognitive-behavioral therapy.

Disclosures: None of the presenters reported having commercial conflicts of interest.

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." ■

Nonveterans Asymptomatic

PTSD *from page 1*

traumatic event," Dr. Pitman said. "They do support the conclusion that the mental disorders found in PTSD result from a trauma."

About one-third of individuals who were exposed to a traumatic event will go on to develop PTSD.

This suggests that certain people might have an underlying predisposition to developing the disorder, Dr. Pitman said.

"We called the twins of the PTSD-affected veterans 'high risk' because they had a shared familial environment and shared genes," he noted.

Indeed, further analysis revealed certain "neurological soft signs" in these twins. "We found subtle abnormalities of the nervous system that were elevated in the veterans with PTSD, [compared with] the veterans without PTSD, and these were also elevated in the identical twins of the PTSD veterans," he reported.

"The nonveterans were not symptomatic; we infer [that] the increased presence of these subtle abnormalities could make them more vulnerable to developing PTSD, but in order for this to occur, there would have to be a traumatic exposure."

When Dr. Harrison G. Pope Jr., coauthor of the 2007 paper that questioned the trauma-PTSD connection, was reached for comment, he said that Dr. Pitman's study was not contradictory to that of Dr. Pope's group. "[Our paper] showed that the symptom cluster of PTSD is not unique to victims of trauma, but can occur commonly in patients seeking treatment for depression, even if these patients have not experienced a trauma," said Dr. Pope, professor of psychiatry at Harvard Medical School, Boston, and director of the biological psychiatry laboratory at McLean Hospital in Belmont, Mass.

VITALS

Major Finding: Symptoms of posttraumatic stress disorder were seen in 50 of 104 Vietnam veterans and in none of their nonveteran identical twins.

Data Source: A study of 104 Vietnam war combat veterans with PTSD (n = 50) and without (n = 54) and their nonveteran identical twins.

Disclosures: The presenters had no conflicts to disclose.

Specifically, Dr. Pope and his colleagues concluded that "the symptom cluster traditionally associated with PTSD may be nonspecific, in that it may frequently occur in the absence of trauma."

By comparison, Dr. Pitman's study "simply showed that trauma can cause these symptoms, to a much greater degree."

From a clinical perspective this means that "one should not automatically assume that all so-called PTSD symptoms are necessarily attributable to trauma. Therefore, when treating a patient who is a trauma victim and who also exhibits symptoms, one should reasonably consider both of these possibilities," he said. ■