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Ketamine Yields Swift Antidepressant Effect in Treatment of Refractory Bipolar Depression

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August 3, 2010 — A single intravenous dose of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine hydrochloride produces a robust antidepressant effect within 40 minutes in patients with treatment-resistant bipolar depression (BPD), according to results of a controlled "proof-of-concept" study published in the August issue of the *Archives of General Psychiatry*.

"What is particularly noteworthy," Carlos A. Zarate, Jr., MD, told *Medscape Medical News*, "is that we demonstrated that it is possible to produce an onset of antidepressant effects in treatment-resistant BPD within 1 hour, which usually takes weeks or longer."

"In my opinion, these results and other related work raise the bar in drug development for BPD in that we should develop treatments that result in an antidepressant response in hours instead of weeks," added Dr. Zarate, who is chief of the Experimental Therapeutics & Pathophysiology Branch, Division of Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland.

Several lines of evidence have recently converged to suggest that dysfunction in the glutamatergic system, particularly the NMDA receptor complex, plays a key role in the pathophysiology of BPD. The new study supports this line of thinking.

The randomized, placebo-controlled, double-blind, crossover, add-on study involved 18 adults with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, BPD resistant to lithium or valproate. The subjects had a mean age of 47.9 years and a mean length of illness of 27.6 years.

They were maintained at therapeutic levels of lithium or valproate and given either an infusion of ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days 2 weeks apart. Thirteen (72%) of the 18 subjects completed both study phases.

The Montgomery-Asberg Depression Rating Scale (MADRS) was used to rate subjects at baseline and at 40, 80, 110, and 230 minutes and on days 1, 2, 3, 7, 10, and 14 after infusion. Change in MADRS score was the primary outcome.

Robust, Rapid Effect

According to the investigators, within 40 minutes, depressive symptoms improved significantly in those receiving ketamine compared with those receiving placebo (d = 0.52; 95% confidence interval [CI], 0.28 – 0.76); this improvement was greatest at day 2 (d = 0.80; 95% CI, 0.55 – 1.04) and remained significant through day 3.

Twelve (71%) of 17 subjects responded to ketamine, and 1 (6%) of 16 responded to placebo at some point during the study, the researchers say, with response defined as 50% improvement from baseline on the MADRS. The median time to response was 40 minutes. Response to ketamine lasted for an average of 6.8 days (SE, 1.4 days); 4 patients responded for 1 week, and 3 additional patients had a response lasting 2 weeks or more.

In addition to the MADRS, statistically significant differences favoring ketamine were also evident on the Hamilton Scale for Depression, the self-rated Beck Depression Inventory, the visual analog scale for depression and anxiety, and the Hamilton Anxiety Rating Scale.

"These findings are particularly noteworthy because a substantial proportion of study participants had been prescribed complex polypharmacy regimens in the past with substantial treatment failures," Dr. Zarate and colleagues note in their report. The average number of past antidepressant trials was 7, and more than 55% of participants failed to respond to electroconvulsive therapy.

The drug was generally well tolerated; dissociative symptoms, only at the 40-minute time point, was the most common adverse effect, a finding "consistent with all published studies using ketamine," the study authors note. Manic symptoms developed in 1 subject receiving ketamine and 1 receiving placebo.

Landmark Contributions

Joseph R. Calabrese, MD, director of the Mood Disorders Program and codirector of the Bipolar Disorders Research Center, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, Ohio, told *Medscape Medical News* that Dr. Zarate "continues to make landmark contributions to the field of mood disorders in general and bipolar disorder in particular.

"His work has shown that increased glutamatergic release results in an almost immediate acute antidepressant response in patients who are in the depressed phase of bipolar I and II disorder. It is the depressed phase of bipolar disorder where our patient live their symptomatic lives, suffer the most, and, in all too many instances, end their life by completing a suicide attempt," added Dr. Calabrese, who was not involved in the current study.

Dr. Zarate and colleagues note that the small size of the study and the inclusion only of the subgroup of patients with treatment-resistant BPD who were relatively late in their illness are 2 limitations of their study. The findings can therefore not be generalized to other patients with BPD with different illness and course characteristics (ie, rapid cycling course and current substance use disorders).

They also say it is possible, although unlikely, that the response seen was due to lithium or valproate rather than ketamine. It is also possible, although again unlikely, they say, that the patients who got better with ketamine had cycled out of their major depressive episode.

The transitory dissociative symptoms seen with ketamine could have compromised the study blinding.

"The primary shortcoming of this research that limits its clinical utility is the method by which ketamine needs to be administered, by intravenous infusions," said Dr. Calabrese. He is hopeful the pharmaceutical industry will "use Dr. Zarate's scientific thesis and now supportive data to develop new treatments that have not only robust short- and long-term efficacy in the depressed phase of bipolar I or II disorder, but now, with almost immediate onset."

The study was funded by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, and by a National Alliance for Research on Schizophrenia and depression Award to Dr. Zarate. A patent application for the use of ketamine in depression has been submitted, listing Dr. Zarate and a coinvestigator among the inventors; they have assigned their rights on the patent to the US government. Dr. Calabrese has disclosed no relevant financial relationships.

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