Ketamine may relieve depression quickly for those with treatment-resistant bipolar disorder

August 2 2010

A single intravenous dose of the anesthetic agent ketamine appears to reduce symptoms of depression within 40 minutes among those with bipolar disorder who have not responded to other treatments, according to a report in the August issue of *Archives of General Psychiatry*.

"Bipolar disorder is one of the most severe psychiatric disorders and ranks in the top 10 causes of medical disability worldwide," the authors write as background information in the article. About 4 percent of Americans will develop bipolar disorder in their lifetimes, and depressive symptoms dominate for most of the course of the illness. Several treatments for bipolar depression are currently approved, but some patients do not respond to these therapies despite adequate trials. In addition, existing treatments are associated with a lag of onset; most patients do not respond within the first week of therapy, resulting in considerable illness and increased suicide risk.

One reason for the lack of better therapies is a limited understanding of the neurobiological basis of bipolar disorder, the authors note. However, recent research suggest dysfunction in the brain's glutamatergic system—which plays a role in information processing and memory formation—may contribute. Nancy Diazgranados, M.D., M.S., and colleagues at the National Institute of Mental Health, Bethesda, Md., assessed the effectiveness of one modulator of this system—ketamine hydrochloride, commonly used as an anesthetic—for bipolar depression.

From October 2006 through June 2009, 18 participants with bipolar depression that had failed to respond to the medications lithium or valproate received an intravenous infusion of either ketamine or a placebo on two test days two weeks apart. The order of the infusions was randomly assigned. Participants were assessed using a depression rating scale before each injection and then 40, 80, 120 and 230 minutes and one, two, three, seven, 10 and 14 days afterward.

Within 40 minutes, those who received ketamine experienced a significant improvement in depressive symptoms compared with those who took placebo, an improvement that was largest at day two and remained significant through day three. At some point during the course of the trial, 71 percent of participants responded to ketamine and 6 percent responded to placebo.

"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," the authors write. "The mean [average] number of past antidepressant trials was seven, and more than 55 percent of participants failed to respond to electroconvulsive therapy. The toll of this protracted and refractory illness on the subjects was evident, in that two-thirds of participants were on psychiatric disability and nearly all were unemployed."

No serious adverse effects were reported during the study. The results lend support to the hypothesis that the glutamatergic system is implicated in the development of bipolar disorder, and that targeting it may lead to improved therapies. "Future research will need to address whether differences in kinetics associated with intravenous administration—which allows for faster absorption and avoids hepatic metabolism—are important or necessary for rapid antidepressant effects to occur," the authors write. In addition, "future studies should examine

strategies for long-term maintenance of ketamine's rapid antidepressant response."

More information: Arch Gen Psychiatry. 2010;67[8]:793-802.

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