New Medication Treats Depression In Hours

Ed. Note: *The following is a press release from the National Institutes Of Health.*

August 7, 2006 -- People with treatment-resistant depression experienced symptom relief in as little as two hours with a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic in humans and animals, in a preliminary study. Current antidepressants routinely take eight weeks or more to exert their effect in treatment-resistant patients and four to six weeks in more responsive patients - a major drawback of these medications. Some participants in this study, who previously had tried an average of six medications without relief, continued to show benefits over the next seven days after just a single dose of the experimental treatment, according to researchers conducting the study at the National Institutes of Health's National Institute of Mental Health.

This is among the first studies of humans to examine the effects of ketamine on depression, a debilitating illness that affects 14.8 million people in any given year. Used in very low doses, the medication is important for research, but is unlikely to become a widely used clinical treatment for depression because of potential side effects, including hallucinations and euphoria, at higher doses. However, scientists say this research could point the way toward development of a new class of faster- and -longer-acting medications. None of the patients in this study, all of whom received a low dose, had serious side effects. Study results were published in the August issue of the *Archives of General Psychiatry.*

"The public health implications of being able to treat major depression this quickly would be enormous," said NIH Director Elias A. Zerhouni, M.D. "These new findings demonstrate the importance of developing new classes of antidepressants that are not simply variations of existing medications."

For this study 18 treatment-resistant, depressed patients were randomly assigned to receive either a single intravenous dose of ketamine or a placebo (inactive compound). Depression improved within one day in 71 percent of all those who received ketamine, and 29 percent of these patients became nearly symptom-free within one day. Thirty-five percent of patients who received ketamine still showed benefits seven days later. Participants receiving a placebo infusion showed no improvement. One week later, participants were given the opposite treatment, unless the beneficial effects of the first treatment were still evident. This "crossover" study design strengthens the validity of the results.

"To my knowledge, this is the first report of any medication or other treatment that results in such a pronounced, rapid, prolonged response with a single dose. These were very treatment-resistant patients," said NIMH Director Thomas R. Insel, M.D.

Ketamine blocks a brain protein called the *N*-methyl-D-aspartic acid (NMDA) receptor. Previous studies have shown that agents that block the NMDA receptor reduce depression-like behaviors in animals.

NMDA receptors are critical for receiving the signals of glutamate, a brain chemical that enhances the electrical flow among brain cells that is required for normal function. Studies indicate that dysregulation in glutamate could be among the culprits in depression. Using ketamine to block glutamate's actions on the NMDA receptor appears to improve function of another brain receptor - the AMPA receptor - that also helps regulate brain cells' electrical flow.

Scientists think the reason current antidepressant medications take weeks to work is that they act on targets close to the beginning of a series of biochemical reactions that regulate mood. The medications' effects then have to trickle down through the rest of the reactions, which takes time. Scientists theorize that ketamine skips much of this route because its target, the NMDA receptor, is closer to the end of the series of reactions in question.

"This may be a key to developing medications that eliminate the weeks or months patients have to wait for antidepressant treatments to kick in," said lead researcher Carlos A. Zarate Jr., of the NIMH Mood and Anxiety Disorders Program.

The researchers who conducted the study now are zeroing in on other areas of the glutamate system. Specifying which components of the system are affected by compounds such as ketamine may help scientists understand how and why depression occurs, reveal biological markers that may one day aid in diagnosis, and point the way to more precise targets for new medications.

Dr. Zarate was joined in this research by Husseini K. Manji, chief of the NIMH Mood and Anxiety Disorders Program, and colleagues Jaskaran B. Singh, Paul J. Carlson, Nancy E. Brutsche, Rezvan Ameli, David A. Luckenbaugh, and Dennis S. Charney.

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