AZD6765 Rapidly Eases Depression

A drug that works through the same brain mechanism as the fast-acting antidepressant ketamine briefly improved treatment-resistant patients' depression symptoms in minutes, with minimal untoward side effects, in a clinical trial conducted by the National Institutes of Health. The experimental agent, called AZD6765, acts through the brain's glutamate chemical messenger system.

Existing antidepressants available through prescription, which work through the brain's serotonin system, take a few weeks to work, imperiling severely depressed patients, who can be at high risk for suicide. Ketamine also works in hours, but its usefulness is limited by its potential for dissociative side-effects, including hallucinations. It is being studied mostly for clues to how it works.

"Our findings serve as a proof of concept that we can tap into an important component of the glutamate pathway to develop a new generation of safe, rapid-acting practical treatments for depression," said Carlos Zarate, M.D., of the NIH's National Institute of Mental Health, which conducted the research.

Zarate, and colleagues, reported on their results online Dec. 1, 2012 in the journal Biological Psychiatry.

AZD6765, like ketamine, works by blocking glutamate binding to a protein on the surface of neurons, called the NMDA receptor. It is a less powerful blocker of the NMDA receptor, which may be a reason why it is better tolerated than ketamine.

About 32 percent of 22 treatment-resistant depressed patients infused with ASD6765 showed a clinically meaningful antidepressant response at 80 minutes after infusion that lasted for about half an hour — with residual antidepressant effects lasting two days for some. By contrast, 52 percent of patients receiving ketamine show a comparable response, with effects still detectable at seven days. So a single infusion of ketamine produces more robust and sustained improvement, but most patients continue to experience some symptoms with both drugs.

However, depression rating scores were significantly better among patients who received AZD6765 than in those who received placebos. The researchers deemed this noteworthy, since, on average, these patients had failed to improve in seven past antidepressant trials, and nearly half failed to respond to electroconvulsive therapy (ECT).

The patients reported only minor side effects, such as dizziness and nausea, which were not significantly different from those experienced with the placebo.

Zarate and colleagues say their results warrant further trials with AZD6765, testing whether repeated infusions a few times per week or higher doses might produce longer-lasting results.

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