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New study shows potential of rational drug design in schizophrenia

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In one of the first instances of targeted drug design in psychiatric treatment, University of Pittsburgh researchers have found an experimental agent that shows promise in addressing working memory impairments that occur in schizophrenia.

The study breaks new ground in the strategy used to develop new pharmacological treatments for schizophrenia, explained David Lewis, M.D., UPMC Endowed Chair in Translational Neuroscience in the departments of psychiatry and neuroscience at the University of Pittsburgh School of Medicine, and lead author of the study that appears in this month's *American Journal of Psychiatry*.

"The drugs we use now to treat psychiatric disorders are based on serendipitous discoveries made several decades ago," he said. "In contrast, in this study we have identified a faulty brain circuit in schizophrenia, found an agent with characteristics that affect a specific molecular target in that circuit, and then tested it to see what happened."

The effectiveness of the experimental drug on cognition was measured with well-established tests of working memory and with EEG, or electroencephalogram, rather than solely with standard clinical assessment.

Earlier research indicated that a reduction of signaling by the neurotransmitter GABA in circuits in an area of the brain called the dorsolateral prefrontal cortex may be to blame for some of the cognitive

problems in schizophrenia, Dr. Lewis explained.

To compensate for the lower levels of GABA, it appears that a biochemical feedback loop increases the number of a specific type of GABA receptor on neurons to capture more neurotransmitter. The study drug, MK-0777, binds to the alpha-2 subunit of the GABAA receptor and, when GABA is present, increases the flow of ions through the receptor, in essence "turning up the volume" on GABA signaling.

For the study, 15 men with schizophrenia between the ages of 18 and 50 were randomly assigned to take either MK-0777 or a placebo for four weeks. They underwent neuropsychological tests at baseline, two weeks and four weeks after starting the drug, as well as an EEG assessment while doing a cognitive task.

The researchers found that participants who took MK-0777 had improvements in both working memory, meaning the ability to keep information in mind to guide behavior, and the EEG signal that accompanies working memory. Also, the drug was well tolerated. Still, because the study is small, more trials will have to be done to verify the value of the experimental compound, Dr. Lewis noted.

Source: University of Pittsburgh