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Drug fights hard-to-treat depression by targeting brain receptors in a new way

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A first-of-its-kind antidepressant drug discovered by a Northwestern University professor and now tested on adults who have failed other antidepressant therapies has been shown to alleviate symptoms within hours, have good safety and produce positive effects that last for about seven days from a single dose.

The novel therapeutic targets brain receptors responsible for learning and memory—a very different approach from existing antidepressants. The new drug and others like it also could be helpful in treating other neurological conditions, including schizophrenia, bipolar disorder, anxiety and Alzheimer's disease.

The results of the phase IIa clinical trial were presented at the 51st Annual Meeting of the American College of Neuropsychopharmacology in Hollywood, Fla.

Also this week a paper reporting some of the background scientific research that provided the foundation for the clinical development of GLYX-13 was published by the journal *Neuropsychopharmacology*.

The compound, called GLYX-13, is the result of more than two decades of work by Joseph Moskal, research professor of biomedical engineering at Northwestern's McCormick School of Engineering and Applied Science and director of the University's Falk Center for Molecular Therapeutics.

"Our study showed that this compound is capable of eliciting a robust and rapid antidepressant effect without the typical side effects seen with other drugs that also modulate the NMDA receptor," said Moskal, who is founder and chief scientific officer of the Evanston-based biotechnology company Naurex Inc., which conducted the clinical study.

GLYX-13 works by modulating the NMDA (N-methyl-D-aspartate) receptor in the brain, as do current NMDA receptor antagonists such as ketamine, but GLYX-13 does not have their serious and limiting side effects, such as hallucinations and schizophrenia-like effects. (An antagonist is a substance that inhibits the physiological action of another.)

Moskal and his team have figured out a new way to target the NMDA receptors that maintains the positive antidepressant properties while eliminating the negative side effects.

In clinical trials administered at 12 sites across the country, a single dose of GLYX-13 resulted in significant reductions in depression symptoms among subjects who had shown little improvement with previous drugs. (Subjects had failed treatment with one or more antidepressant agents.)

The positive effects of GLYX-13 were evident within 24 hours and lasted an average of seven days. The effect size, a measure of the magnitude of the drug's antidepressant efficacy, at both these times after a single dose was nearly double the effect size seen with most other antidepressant drugs after four to six weeks of repeated dosing.

Side effects of GLYX-13 were mild to moderate and were consistent with those observed in subjects receiving a placebo.

GLYX-13 is a four-amino acid peptide that modulates one of a large family of glutamate receptors, the NMDA (N-methyl-D-aspartate)

receptor, in the brain. NMDA receptors play a key role in regulating synaptic plasticity—the quality of the connection between neurons—and thus are important in regulating learning and memory functions.

GLYX-13 is administered intravenously. Moskal said Naurex also is working on an oral drug with similar properties and potential.

Moskal hopes that these positive GLYX-13 results and the research efforts of his team and colleagues will help shepherd in more research and grant support for studying the role of the glutamate-mediated processes in neuropsychiatric disorders.

"While the results we are seeing with GLYX-13 are very encouraging, I believe the most important research is yet to come," Moskal said. "We have only scratched the surface of the therapeutic potential of the glutamatergic system."

GLYX-13 currently is undergoing a phase IIb clinical trial at 20 sites across the United States. This trial is evaluating repeated doses of the drug.

The Neuropsychopharmacology paper is titled "GLYX-13, an NMDA Receptor Glycine-Site Functional Partial Agonist, Induces Antidepressant-Like Effects Without Ketamine-Like Side Effects."

More information: www.nature.com/npp/journal/vao … abs/npp2012246a.html

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