Antidepressant with novel action appears safe and effective in phase 1b clinical trial

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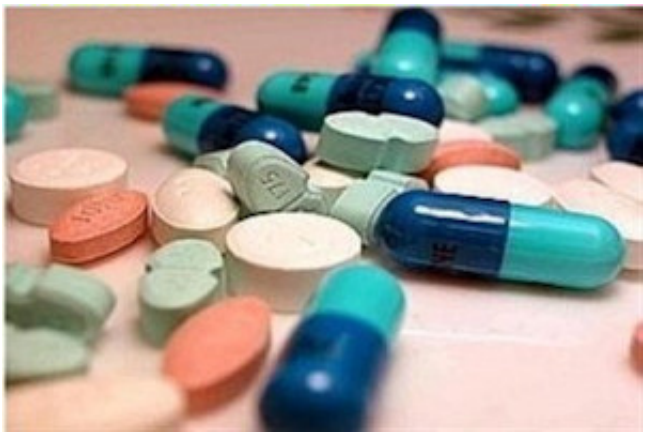

Various pills. Credit: Wikipedia

A small clinical trial of a novel antidepressant that stimulates neurogenesis - the production of new brain cells - shows that the compound appears to be safe and may be effective against depression. Results of the phase 1B trial, led by Massachusetts General Hospital (MGH) investigators, show that treatment with the drug currently identified as NSI-189 improved both depressive and cognitive symptoms in study participants and that its effects appear to persist for several months after treatment discontinuation. The study was supported by the pharmaceutical company Neuralstem.

"All currently approved antidepressant drugs modulate changes in the levels of monoamine neurotransmitters," says Maurizio Fava, MD,

executive director of the Clinical Trials Network & Institute (CTNI) in the MGH Department of Psychiatry, lead author of the study published online in the journal *Molecular Psychiatry*. "Our study finds that this novel compound promotes neurogenesis in a specific part of the brain, is well tolerated and may have robust antidepressant effects. If its efficacy is confirmed in larger trials, this drug could be an important new option for patients not helped by currently available medications."

The study authors note that only one third of patients with major depressive disorder can be adequately treated with today's antidepressant drugs. For some, the drugs do not provide sufficient symptom relief; for others, unpleasant side effects - including gastrointestinal symptoms, weight increase, sleep disorders and sexual dysfunction - can lead them to discontinue treatment. While the primary mechanism of current antidepressants is alteration of neurotransmitters like serotonin, these drugs also induce neurogenesis in the brain structure called the hippocampus, suggesting that increasing neurogenesis could be an alternate strategy for treating depression.

Animal studies of NSI-189 conducted by Neuralstem, which is developing the drug for clinical use, showed that it stimulated hippocampal neurogenesis and improved behavioral symptoms in a mouse model of depression. A phase 1a trial in healthy volunteers was conducted in 2011, and the current phase 1b trial - designed primarily to address safety and identify the maximum safe dose - was designed and guided by investigators from the MGH CTNI. The trial enrolled 24 adult patients diagnosed with major depressive disorder, who were randomized into three treatment groups. In each group of 8 participants, 6 received the active drug and 2 received a placebo; those assigned to the active drug in the double-blinded study received 40 mg doses either once, twice or three times daily. After 28 days of treatment, which was conducted in an inpatient clinical trials unit, patients were followed for another 56 days.

Reports of adverse effects - none of them serious - were similar in both the control group and in participants receiving the active drug, even those who took the maximum daily dose. EEG readings taken prior to and at several times during treatment showed some changes, primarily an increase in high-frequency alpha waves, and MRI scans suggested the possibility of increased hippocampal volume in those taking the active drug. On four measures of depressive or cognitive symptoms, participants receiving the active drugs showed improvement after the 28-day treatment period, with significant differences from the placebo group on two measures based on participants' self-reports. Symptom improvement was maintained throughout the follow-up period, which the authors indicate is particularly notable since the effects of current antidepressants typically only last as long as they are taken. The MGH team has also helped to design and is involved in implementing the larger phase 2 trial of NSI-189 that has recently been initiated

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