A new generation of rapid-acting antidepressants?

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Conventional antidepressant treatments generally require three to four weeks to become effective, thus the discovery of treatments with a more rapid onset is a major goal of biological psychiatry. The first drug found to produce rapid improvement in mood was the NMDA glutamate receptor antagonist, ketamine.

In a new issue of Biological Psychiatry researchers from the National Institutes of Health report that another medication, scopolamine, also appears to produce replicable rapid improvement in mood. Scopolamine temporarily blocks the muscarinic cholinergic receptor, thought to be overactive in people suffering from depression.

Drs. Wayne Drevets and Maura Furey recruited outpatients with major depressive disorder who were randomly assigned to receive placebo and then scopolamine treatment, or vice versa, in a double-blinded design so that neither the researchers nor the patients knew which treatment they were receiving.

"Scopolamine was found to reduce symptoms of depression within three days of the first administration. In fact, participants reported that they experienced relief from their symptoms by the morning after the first administration of drug," explained Dr. Furey. "Moreover, one-half of participants experienced full symptom remission by the end of the treatment period. Finally, participants remained well during a subsequent placebo period, indicating that the antidepressant effects persist for at least two weeks in the absence of further treatment."

The efficacy of scopolamine is very interesting because the potent blockade of muscarinic receptors was a property of tricyclic antidepressant medications, the oldest type of antidepressants. With these medications, the muscarinic receptor blockade was mostly viewed as the cause of unwanted side effects, such as constipation, sedation, and memory impairments. Newer antidepressants, such as serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, were explicitly designed to avoid blocking muscarinic receptors. Yet, the current data raise the possibility that this strategy may have increased safety and tolerability of these medications at the expense of providing effective and timely relief for depression symptoms.

Dr. John Krystal, Editor of *Biological Psychiatry*, commented that these findings "have the potential to raise expectations for new antidepressant treatments. Three-to-six weeks is a long time to wait for depression symptoms to be alleviated. Depressed people describe their emotional state using terms like 'agony' and others compare their condition to 'living in hell'. Further, depression is a life-threatening condition for some, preventing them from performing basic self-care functions or causing them to exhibit self-destructive behavior."

Although these findings open the door to a conceptually different approach to the treatment of depression, it remains to be seen whether rapid acting antidepressant effects will be viable clinically. One could imagine that they might mitigate hospitalization in some patients and enhance the overall effectiveness of the treatment of depression. However, this possibility remains to be demonstrated empirically in studies that show that a rapid-acting antidepressant treatment can be smoothly transitioned to definitive long-term treatment for depression.

More information: The article is "Replication of Scopolamine's Antidepressant Efficacy in Major Depressive Disorder: A Randomized, Placebo-Controlled Clinical Trial" by Wayne C. Drevets and Maura L.

Furey. The authors are affiliated with the Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland. The article appears in Biological Psychiatry, Volume 67, Issue 5 (March 1, 2010).