Why is it so hard to withdraw from some antidepressants?

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Researchers at the University of Illinois Chicago are a step closer to discovering why it is so difficult for people to withdraw from some antidepressant medications.

The paper, "Antidepressants produce persistent G?s associated signaling changes in lipid rafts following drug withdrawal," published in the journal *Molecular Pharmacology*, addresses the molecular and cellular mechanisms that cause antidepressant withdrawal syndrome.

The study's authors, Mark Rasenick, distinguished professor of physiology and biophysics and psychiatry at UIC and research career scientist at the Jesse Brown VA Medical Center, and Nicholas Senese, a postdoctoral fellow at UIC, explained that current antidepressants can take approximately two months to take effect in patients who then continue taking these drugs for years. Weaning patients from these drugs can result in unpleasant symptoms that can range from flu-like feelings and persistent pain or itch to Parkinson's-like conditions that can last for weeks.

One in six Americans have, or will, suffer from depression; for veterans, the estimated rate is twice that.

Previous research has demonstrated that antidepressant drugs collect gradually in cholesterol-rich membrane structures called lipid rafts. When a neurotransmitter (such as serotonin, which is involved with mood) binds to a receptor on the outside of a cell, a protein in the lipid raft —— called Gs alpha —— conveys the signal into the cell's interior where it can elicit a variety of actions. One of those actions is the production of an intracellular signaling molecule called cyclic AMP. In the brains of people with depression, cyclic AMP is low; but with effective antidepressant treatment, cyclic AMP is returned to normal.

For their new study, Rasenick and Senese looked at the activity of Gs alpha molecules by using fluorescent light to determine how they moved in and out of the lipid rafts. They found that while withdrawal of some antidepressant drugs balances Gs alpha action in and out of the lipid rafts, other drugs suppress the return of Gs alpha to rafts. This suppression, the researchers believe, is what causes persistent and undesired effects of some antidepressants.

Lipid rafts appear to be relevant for both the delayed therapeutic effects of antidepressants as well as the difficulty in weaning off from these drugs. It takes a long time for these drugs to sort into rafts and a long time for the drugs to exit —— some more than others. Curiously, rapid-acting antidepressants like ketamine have similar effects on Gs alpha and lipid rafts, but without the delay, Rasenick said.

"This validates the notion that intracellular molecules that result from an active Gs alpha protein are a very good biomarker for the functioning of antidepressants," Rasenick said. "We think we have achieved some clarity on this issue

and we'd like to move forward toward using technology to create a personalized treatment for depression."

Rasenick explained that by looking at how an individual patient's cells metabolize Gs alpha proteins, they can better predict what antidepressant medication could work for them. This can be accomplished in days and not weeks and months of trial and error to find the right medication. A company using this UIC-developed technology, Pax Neuroscience, has been formed to develop the technology for the market.

More information: Nicolas B. Senese et al, Antidepressants produce persistent G?s associated signaling changes in lipid rafts following drug withdrawal, *Molecular Pharmacology* (2021). DOI: 10.1124/molpharm.120.000226

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