FDA warning against high dose antidepressant prescription may be unwarranted, study finds

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The U.S. Food and Drug Administration's warning that high doses of the antidepressant citalopram can cause potentially serious abnormal heart rhythms might be doing more harm than good.

In 2011, the FDA attached a warning to the drug, also known as Celexa, based on data linking higher doses of the drug to potentially fatal abnormal changes in the electrical activity of the heart.

The new Ann Arbor VA Healthcare System and University of Michigan study, however, calls into question the FDA's warning after finding no increased risk for abnormal heart rhythms or death in patients who took daily doses of more than 40 milligrams before or after the warning took effect.

Since the warning went into effect, physicians have begun to limit citalopram prescriptions, even though higher doses can offer relief to some high-risk depression patients.

The study, which was published online today in the *American Journal of Psychiatry*, is the largest analysis to date of outcomes related to citalopram use.

"Our findings raise questions about the continued legitimacy of the FDA warning and provide support for the question of whether the warning will do more harm than good," says Kara Zivin, Ph.D., assistant professor of psychiatry at U-M, research investigator at the VA Center for Clinical Management Research (CCMR) and the study's lead author.

Helen Kales, M.D., associate professor of psychiatry, research investigator at CCMR, and the study's senior author added, "For some patients, a dosage higher than 40 milligrams per day can be very beneficial. Unfortunately the FDA's warning may have made attaining such a prescription more difficult."

The researchers analyzed data from more than 600,000 Veterans Health Administration patients who received citalopram prescriptions between 2004 and 2009. The study also examined patient outcomes for more than 300,000 patients who were prescribed a similar antidepressant, sertraline, which does not have an FDA warning.

Results indicated no elevated risks of ventricular arrhythmia or death related to higher dosages of citalopram. In fact, higher dosages were associated with fewer adverse outcomes than lower dosages. Similar findings were observed in the comparison drug sertraline, which is prescribed without warning.

Zivin says additional exploration into the possible link between citalopram and cardiac risks will be necessary to provide further guidance to clinicians who are considering the drug for their patients. The new results, which appear to contradict the basis for the FDA's warning, present clinicians with a conundrum.

For example, Zivin notes, physicians may wonder, "Should dosages be modified for those with risk factors for cardiac complications? Should health care providers alter how they prescribe this drug to new patients, or order ECGs for patients at risk before writing a new prescription? Or should patients be switched to other antidepressants with similar profiles, but no warning? These are all things clinicians need to consider."

She adds, "Currently, clinicians whose patients benefit from high dosages of citalopram must choose between following the FDA's warning or

risking worsening depression if patients receive too low a dosage."

Zivin says she and her research group are exploring options for further studies examining how the warning has influenced patients' use of the drug.

More information: "Evaluation of the FDA Warning Against Prescribing Citalopram at Doses Exceeding 40 mg" *American Journal of Psychiatry* (2013)

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