Study clarifies antidepressant contribution to arrhythmia risk

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A 2011 warning from the U.S. Food and Drug Administration about the popular antidepressant citalopram (Celexa) left many patients and physicians with more questions than answers. Now an analysis of the medical records of more than 38,000 patients by Massachusetts General Hospital (MGH) investigators clarifies the contribution of citalopram and other antidepressants to lengthening of the QT interval, an aspect of the heart's electrical activity that – when prolonged – may increase the risk of dangerous arrhythmias. The study supported the FDA's warning that higher doses of citalopram were associated with a prolonged QT interval but also found that the effects of some other antidepressants were quite different.

"It was important to confirm the effects of citalopram – one of the most widely prescribed antidepressants in the U.S. – because the FDA warning really gave us minimal clinical guidance," says Roy Perlis, MD, of the MGH Department of Psychiatry, corresponding author of the report that will appear in the journal BMJ and is being released online. "The impetus for this study came directly from the phone calls we received from colleagues and from patients taking citalopram asking what they should do. We realized that to get a satisfying answer, we needed to get more data."

Many medications – including some older antidepressants – are known to increase the QT interval, which is the time from the beginning of electrical activation of the heart to the end of electrical relaxation. While the vast majority of individuals with QT prolongation have no heart

rhythm abnormalities, it is a recognized risk factor for a rare but dangerous arrhythmia called torsades de pointes. To get a better idea of the real-world prevalence of QT prolongation associated with citalopram and other antidepressants, the MGH team embarked on an analysis of the medical records of thousands of patients treated at the MGH and other Partners HealthCare facilities.

"We are fortunate that our colleagues at MGH and Partners have developed incredibly useful tools to answer specific questions by rapidly and simultaneously looking across electronic health record data from tens of thousands of patients while protecting patient confidentiality," Perlis explains. "Working with them we developed a way to look at each EKG report and pull out QT interval information and other relevant results. Doing this by hand – flipping through individual patient charts – would have taken a year or more. Doing it with electronic health records took about an hour."

The study examined the health records of 38,397 patients who had an EKG reading taken at a Partners facility between 14 and 90 days after receiving a prescription for one of 11 different antidepressant drugs or for methadone, which is known to prolong QT interval. Their analysis confirmed the association of a slight but significant QT prolongation with higher doses of citalopram, along with the known associations with methadone and with the older antidepressant amitriptyline. The results also associated QT prolongation with the newer antidepressant escitalopram (Lexapro); but many other drugs – including fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft) – had no effect on QT interval. The antidepressant bupropion (Wellbutrin/Zyban) was actually associated with shortening the QT interval.

Perlis cautions that the results of this study should not cause patients taking citalopram or escitalopram to stop taking their medication. "I worry more about people stopping their antidepressants unnecessarily

than about the QT prolongation risks," he explains. "For patients starting a new antidepressant who have other risk factors for arrhythmias, a drug other than citalopram would probably be a wise choice. But for those already taking lower doses of either of these drugs, the QT prolongation effects seem to be modest. The real message to patients taking these drugs is to have a conversation with their doctors."

The speed with which the investigators were able to complete their study reflects the power of electronic health record analysis to answer important research questions, he adds. "Finding the QT-shortening effects of bupropion shows how this approach can help us find drugs with unexpected benefits and not just unexpected problems. As long as we're willing to accept the limitations – particularly the fact that people aren't randomly assigned to different treatments – this strategy allows us to study many more patients and get answers much faster. In terms of patient privacy, this is actually much safer than the older methods, which required a person to look through a pile of medical records one by one. This way we only extract the data we need and never see anything that would allow us to identify an individual patient." Perlis is an associate professor of Psychiatry at Harvard Medical School.

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