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Citalopram and QT Prolongation

New evidence on monotherapy with citalopram suggests less risk than previously thought – even for doses higher than 40mg

In August, 2011, the FDA added a warning to citalopram labeling, indicating a risk of QT prolongation and Torsade de Pointes (TdP) especially at doses higher than 40mg per day 1. Health Canada also released a similar warning in January, 2012 2. Advisories like these can drastically change medication prescribing patterns, often causing appropriate use to decrease alongside inappropriate use 3, so their reliability and accuracy are paramount. The citalopram warnings have gone mostly unchallenged since the original data was published; however, a recently completed, large cohort analysis found no increased risk of ventricular arrhythmia, cardiac mortality or all-cause mortality with high dose citalopram (greater than 40mg) compared to low doses (less than 20mg), casting some doubt on the clinical importance of the Health Canada and FDA warnings 4.

The new evidence is from an observational cohort study analyzing 618,450 individuals, predominantly male (90.4%) with an average age of 57 years, who received any amount of citalopram between 2004 and 2009. 18.6% of patients received high dose citalopram (more than 40mg); 51.5% received medium dose (21-40mg); 29.9% received low dose (1-20mg). The patients were followed until they had any of the predetermined outcomes: paroxysmal ventricular tachycardia, ventricular fibrillation, ventricular flutter, cardiac arrest, or all-cause, cardiac or non-cardiac mortality. A cohort of sertraline users was included to offer a comparison with an SSRI without a QT prolongation warning.

Some of the results are summarized below; bolded outcomes are statistically significant hazard ratios with a 95% CI compared to low-dose citalopram (1-20mg) 4:

Outcome	Citalopram (21-40mg)	Citalopram (>40mg)	Sertraline (>100mg)	Received concomitant medication with risk of TdP (any dose of citalopram)
Ventricular arrhythmia	**0.80 (0.74-0.86)**	**0.68 (0.61-0.76)**	**0.70 (0.62-0.78)**	**1.32 (1.22-1.42)**
All-cause mortality	0.97 (0.94-1.00)	**0.94 (0.90-0.99)**	1.0 (0.96-1.04)	**1.22 (1.19-1.26)**
Cardiac mortality	0.98 (0.94-1.04)	1.03 (0.95-1.11)	1.03 (0.96-1.11)	**1.19 (1.13 – 1.25)**
Non-cardiac mortality	0.97 (0.93 – 1.0)	**0.90 (0.86 – 0.96)**	0.98 (0.93-1.03)	**1.24 (1.20-1.29)**

The authors conclude there is no increased risk of arrhythmias, cardiac mortality or all-cause mortality with higher doses of citalopram, versus a low dose. The data, in fact, shows a protective effect on arrhythmia and mortality at higher doses, but the authors do not conclude high dose citalopram has mortality benefit, citing a number of possible confounding factors. For example, older, frailer patients were more likely to receive a low dose of citalopram, but had a higher risk of death, thus making mortality rates higher in the low dose citalopram group.

In contrast to monotherapy, citalopram use at any dose in combination with a medication with a known risk for TdP did show an increase in negative outcomes. It is unclear whether the citalopram, the other drug, or the combination of the two was the culprit; however, current knowledge indicates the risk of TdP is additive when drugs which increase the QT-interval are taken concurrently 5. While citalopram alone does not appear to increase the risk of negative outcomes, it does increase the QT interval 1, therefore the combination of citalopram and other high risk drugs is still a concern.

The study does have some limitations. There is no placebo group, so the background rate of the end-points is unknown. Also, the cohort was 90.5% males. Females have a higher risk of developing drug-induced Torsade de Pointes (TdP) 6, thus the results may not be generalizable to women.

The FDA's warning is based on post-marketing reports of QT-prolongation and TdP associated with citalopram, and a small (N=119), randomized, double-blind, placebo-controlled, cross-over study. The study found citalopram 20mg/day increased the QT interval by 8.5ms while a dose of 60mg/day increased it by 18.5ms. However, the study did not determine if these increases were clinically relevant or increased the risk of TdP. The FDA concluded citalopram in doses of more than 40mg/day significantly increases the QT interval and has no evidence for added benefit, and therefore should no longer be prescribed at high doses 1. In response to criticism that a 18.5ms QT-interval increase is likely a negligible risk for TdP in most patients, the FDA reiterated that there is no evidence supporting the use of 60mg instead of 40mg or lower, even in patients not responding to the 40mg dose; thus, the potential risk outweighs the questionable benefit of a 60mg dose 7.

When comparing the two bodies of conflicting evidence (FDA and Zivin et al.), the new analysis, even though observational, was a much larger study. Most importantly, the study examined clinical outcomes with citalopram use, rather than just the surrogate endpoint of the QT-prolongation. Although the QT-interval is an important measure for possible negative outcomes, the exact risk of TdP induction is unknown.

This raises some important questions. Should ECG monitoring still be recommended for patients receiving higher doses of citalopram? How many risk factors (electrolyte imbalance, congenital long QT interval, concomitant medications that increase QT interval, female sex, old age, atrial fibrillation, underlying heart disease, recent MI 5) for TdP need to be present before citalopram use becomes a concern? Should patients be switched to a different anti-depressant in some cases?

It is reasonable to avoid citalopram in doses greater than 40mg/day; even though it does not appear to cause negative clinical outcomes, it does increase the QT-interval 1**. Some patients have responded to higher doses of citalopram when a 40mg dose has failed** 8**, so weighing the risks vs. benefits is important. Switching patients to a different SSRI, or recommending an ECG in the absence of other risk factors, is not necessary. However, citalopram in combination with other QT-prolonging drugs does appear to increase risk for TdP, so intervention, especially in the presence of other risk factors, should be considered. If the risk of TdP is a concern and an anti-depressant is needed, other SSRIs (sertraline, paroxetine, fluoxetine), bupropion and venlafaxine do not increase the QT-interval** 9**.**

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