

# REVIEW

## Risk Assessment of QT Prolongation with Citalopram and Escitalopram: An Evidence Based Review

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### Abstract

Recent health advisories have identified a risk of QT prolongation with the commonly used antidepressants citalopram (Celexa®) and escitalopram (Cipralex®). Pertinent literature was searched for, uncovered, and critically assessed to determine the comparative risk of arrhythmias or death between citalopram and escitalopram. No data were found directly addressing our clinical question by evaluating the two antidepressants for their comparative risk. However, several randomized and crossover trials, as well as a cohort study, were found to address questions regarding the cardiovascular risk of each agent. Available studies indicate a dose-related lengthening of the QT interval with both antidepressants, suggesting that these agents should be used at lower doses in patients with risk factors for arrhythmias. Overall, the evidence suggests that there is no clear advantage to using escitalopram in place of citalopram to minimize the risk of QT prolongation resulting in fatal arrhythmias.

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Citalopram and escitalopram have been the subject of several Health Canada and U.S. Food and Drug Administration (FDA) advisories issued since August 2011.<sup>1-5</sup> They raise concern over the potential for these agents to cause QT prolongation. Excessive lengthening of the heart rate-corrected QT (QTc) interval may in rare cases induce Torsade de Pointes (TdP), a tachyarrhythmia associated with ventricular fibrillation, cardiac arrest, and in about 10 to 17% of cases, death.<sup>6,7</sup> As patient heart rhythm is not continuously monitored and death occurs rapidly, measuring the rate of TdP and the resulting mortality is exceptionally difficult, especially in the outpatient setting.<sup>8</sup>

In adults, the normal QTc interval is <430 msec in males and <450 msec in females.<sup>9</sup> Prolongation above 450 msec and 470 msec in males and females, respectively, has been estimated to be associated with a two- to threefold increased risk of sudden cardiac death.<sup>8-10</sup> Risk factors for QTc prolongation or arrhythmias include taking multiple QTc prolonging medications, age greater than 65 years, heart disease, electrolyte imbalances, and decreased systemic clearance of QTc-prolonging drugs.<sup>11-15</sup>

Case reports and cross sectional studies suggest that QTc prolongation with citalopram and escitalopram is dose-related.<sup>16,17</sup> To address this concern, federal bulletins have recommended that daily doses of citalopram and escitalopram should not exceed 40 mg and 20 mg, respectively, and that both agents be used at the lowest effective dose or avoided entirely in patients with risk factors.<sup>1,5</sup>

Escitalopram, the (S)-enantiomer of citalopram, is given at a lower dose than the racemic mixture while maintaining efficacy in the treatment of unipolar depression.<sup>18-20</sup> The question as to whether this translates into a decreased risk of QTc prolongation remains unanswered. This report endeavors to determine if escitalopram has evidence to suggest its use in place of citalopram to lower the risk of QTc prolongation-related morbidity and mortality in adult patients with cardiovascular risk factors.

### Clinical Question

In a middle-aged patient with the QTc prolonging risk factor of heart disease and recurrent major depressive disorder previously responsive to citalopram, is escitalopram an effective and safe option compared to citalopram to induce remission of depression while minimizing the risk of a serious and potentially fatal arrhythmia?

### Search Strategy

The Cochrane Library, PubMed, EMBASE, and ClinicalTrials.gov were searched for studies pertinent to the clinical question. The keywords “citalopram”, “serotonin uptake inhibitor”, “long QT syndrome”, and “cardiac arrhythmia” were used as medical search headings (MeSH). Searches of titles and abstracts were conducted using keywords and additionally the terms “escitalopram”, “selective serotonin reuptake inhibitor”, “QTc”, and “QT prolongation”. Three assessors independently analyzed titles and abstracts of retrieved articles, and deemed 43 articles from EMBASE and three articles from PubMed, as potentially contributory to the question. These studies discussed

QTc prolongation or arrhythmias in the context of citalopram or escitalopram.

We excluded non-English articles, trials reporting non-quantitative or unusable data<sup>21</sup>, and studies examining only acute overdoses (Figure 1).<sup>22</sup> Searching references of the included articles yielded two additional studies that were relevant to the case.<sup>23,24</sup> Using Web of Science, we searched for relevant reviews and articles citing the selected studies.<sup>16,25,26</sup>

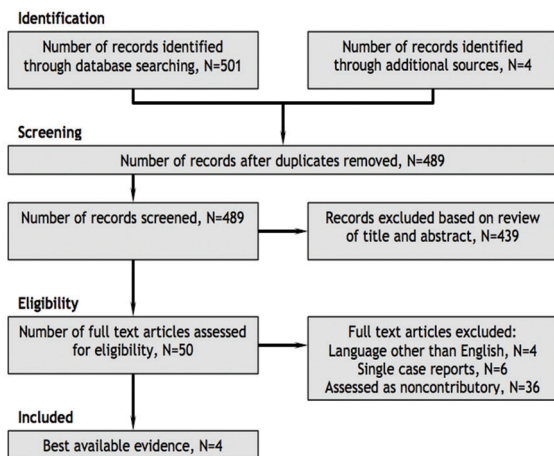


Figure 1. Search strategy and findings.

## Results

Two randomized controlled trials (RCTs), two crossover studies, and one cohort study were considered as the best evidence addressing the clinical question (Table 1). The FDA summarized the results of two unpublished crossover studies assessing QTc prolongation with citalopram and escitalopram.<sup>5</sup> RCTs by Hanash et al.<sup>27</sup> and Lespérance et al.<sup>23</sup> investigated escitalopram and citalopram therapy in patients with cardiovascular disease. The study by Leonard et al. assessed clinical outcomes of ventricular arrhythmia and sudden death (VA/SD) in a large cohort of antidepressant users.<sup>24</sup>

In each blinded crossover trial analyzed by the FDA, subjects received sequential therapy of increasing doses of citalopram or escitalopram, followed by moxifloxacin and placebo.<sup>5</sup> Citalopram 20 mg/day increased QTc duration by a mean of 8.5 msec (90% CI, 6.2 to 10.8) from baseline. Escitalopram 10 mg/day showed a mean change in QTc duration of 4.5 msec (90% CI, 2.5 to 6.4). Based on the results, we calculated the standard deviation estimating the upper

limit of change in QTc duration. While this may not accurately represent the risk in clinical practice, theoretically 1 of every 40 patients taking citalopram 20 mg/day may have a QTc duration increase of 39.1 msec from baseline. Comparatively, 1 of 40 patients taking escitalopram 10 mg/day may experience a QTc duration increase of 29.7 msec. Moxifloxacin 400 mg/day showed a mean increase of 13.4 msec (90% CI, 10.9 to 15.9) in the citalopram study and 9.0 msec (90% CI, 7.3 to 10.8) in the escitalopram study. The variability in moxifloxacin's effect indicates that the degree of QTc prolongation between citalopram and escitalopram may be more similar than suggested by these studies' results (Figure 2).

The FDA did not report cases of TdP or QTc changes with placebo. The inability to assess study details and patient characteristics, limits the inferences that can be drawn. The findings suggest a dose-dependent increase in QTc duration with both citalopram and escitalopram and neither agent appears safer at comparable doses. A >30 msec lengthening of the QTc interval or a duration >500 msec suggests an increased risk of arrhythmias including TdP.<sup>9</sup> The subsequent risk of mortality in about 1 of 40 patients taking citalopram or escitalopram may be clinically significant for those with QTc prolonging risk factors.

In a 12-month RCT by Hanash et al., escitalopram 10 mg/day was compared to placebo in 240 adults with acute coronary syndromes (ACS) for prophylaxis of depression.<sup>27</sup> ECG measurements showed no difference in QTc duration between the groups at six months and 12 months ( $P>0.10$ ). The overall incidence of major cardiac events was not significantly different between escitalopram and placebo (13.3% vs. 10.9%;  $P=0.59$ ). Major cardiac events included recurrent acute coronary syndrome (7.5% in the escitalopram group vs. 4.2% in placebo group;  $P=NS$ ), need for acute revascularization (5.0% vs. 2.5%;  $P=NS$ ), and death (5.0% vs. 3.3%;  $P=NS$ ).

Lespérance et al. conducted a parallel group RCT comparing citalopram 20 to 40 mg with matching placebo in 284 adults diagnosed with coronary artery disease (CAD) and depression.<sup>23</sup> No statistically significant difference was found in mean QTc duration between citalopram and placebo after 12 weeks ( $P=0.18$ ) and no cases of serious QTc prolongation (>525 msec) were reported. This confirms that the 1 in 40 risk of potentially clinically significant QTc prolongation is likely exaggerated from the theoretical assumptions extrapolated from the FDA studies.

Table 1: Summary of best available evidence: QTc prolongation, arrhythmias, and sudden cardiac death with citalopram and escitalopram.

Study	Design	N	Participants	Intervention	Follow-up	Results
FDA report: QTc prolongation and citalopram (2011) <sup>5</sup>	Blinded, PC, crossover study	119	Adults, details unknown	Each patient received citalopram (20 mg/day and 60 mg/day), moxifloxacin 400 mg/day, and placebo	Unknown	Mean change (90% CI) in QTc interval (msec): Citalopram 20 mg: 8.5(6.2-10.8) Citalopram 60 mg: 18.5(16.0-15.9) Moxifloxacin 400 mg: 13.4(10.9-15.9) Placebo: n/a
FDA report: QTc prolongation and escitalopram (2011) <sup>5</sup>	Blinded, PC, crossover study	113	Adults, details unknown	Each patient received citalopram (20 mg/day and 60 mg/day), moxifloxacin 400 mg/day, and placebo	Unknown	Mean change (90% CI) in QTc interval (msec): Escitalopram 10 mg: 4.5(2.5-6.4) Escitalopram 30 mg: 10.7(8.7-12.7) Moxifloxacin 400 mg: 9.0(7.3-10.8) Placebo: n/a
Hanash et al. (2012) <sup>27</sup>	R, DB, PC	240	Adult patients, non-depressed (HAM-D <13), hospitalized for ACS	1 year treatment with either escitalopram 10 mg/day or matching placebo	Cardiac assessments at baseline, 6 months, and 12 months. Ambulatory 24-hour ECGs.	Mean QTc interval (msec) at baseline vs. 12 month follow-up (SD): Escitalopram: 399(26) vs. 396(29) Placebo: 398(35) vs. 388(19) Patients at baseline vs. 12 months with QTc interval >450 msec: Escitalopram: 5.0% vs. 2.5% Placebo: 5.0% vs. 0.0% One year incidence of major cardiac events, escitalopram vs. placebo: 13.3% vs. 10.9% (p=0.59)
Leonard et al. (2011) <sup>24</sup>	Cohort study, 1999-2003	3,397,470 (citalopram: 294,434, paroxetine: 560,822)	Medicaid enrollees	Exposures: SSRIs, SNRIs, TCAs, lithium, and others Control: paroxetine	Incident first-listed ER or inpatient diagnosis of SD/VA	Crude incidence rate of SD or VA per 1000 person-years (95% CI): Citalopram: 3.6(3.29-3.94) Paroxetine: 3.15(2.93-3.38) Data unavailable for adjusted hazard ratio.
Lespérance et al. (2007) <sup>23</sup>	Multicenter, RCT, 12-week, parallel-group, 2 x 2 factorial trial	284	Adult patients (mean age: 58.3), established CAD, major depression (HAM-D ≥20) for 14 weeks at baseline	2 separate randomizations: 1) Clinical management with or without IPT 2) 12 weeks of citalopram 20-40 mg/day (mean dose: 33.1 mg/day) or matching placebo	ECG at baseline and 12 weeks	Mean QTc interval (msec) at baseline vs. 12 week follow-up (SD): Citalopram: 416.3(27.36) vs. 418.1(23.77) Placebo: 416.4(19.59) vs. 415.1(17.03) No evidence of difference in QTc interval between citalopram and placebo groups (p=0.18) No QTc prolongation >525 msec in either intervention

ACS: acute coronary syndromes, CAD: coronary artery disease, CI: confidence interval, DB: double blind, ECG: electrocardiogram, ER: emergency room, FDA: U.S. Food and Drug Administration, HAM-D: Hamilton Rating Scale for Depression, IPT: inter-personal therapy, PC: placebo-controlled, QTc: heart rate-corrected QT interval, R: randomized, RCT: randomized controlled trial, SD/VA: sudden death or ventricular arrhythmia, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin norepinephrine reuptake inhibitor, TCA: tricyclic antidepressant, TdP: Torsade de Pointes

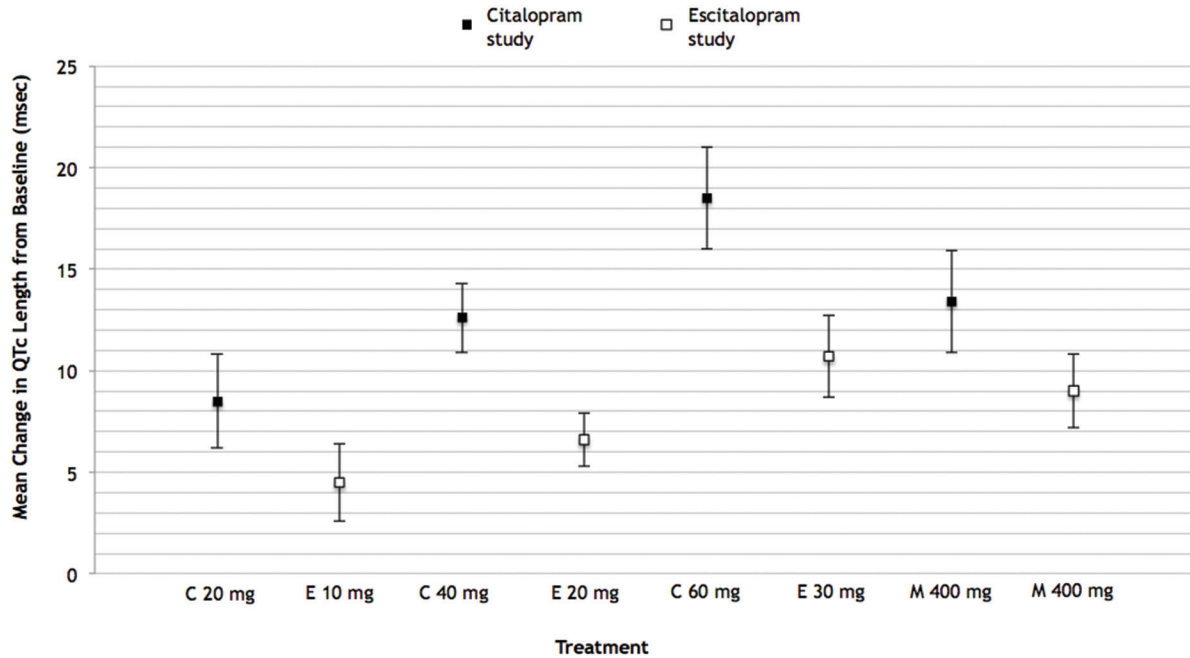


Figure 2. FDA study: 90% confidence intervals of mean QTc interval change with citalopram, escitalopram, and moxifloxacin.<sup>5</sup>

Hanash et al. and Lespérance et al. performed RCTs with adequate sample sizes to address efficacy of their intervention.<sup>23,28</sup> However, when assessing the secondary outcome of clinical QTc prolongation both studies lacked adequate power, suggesting an overall inability to detect QTc changes at therapeutic doses. These studies contradict the FDA’s findings that citalopram and escitalopram are associated with significant QTc changes.<sup>5</sup>

Leonard et al. completed a cohort study of over 3 million patients to examine the association between antidepressant exposure and hospital admission for VA/SD.<sup>24</sup> Paroxetine was selected as the reference exposure to limit potential confounding by indication (depression) and due to its limited effect on the QTc interval. The unadjusted incidence rate ratio of 1.14 (95% CI, 1.02 to 1.28) versus paroxetine suggested that exposure to citalopram may carry a slightly higher risk of VA/SD (Relative Risk=14%). However, after adjusting for potential confounders, including age, sex, and nursing home residence, no difference in hazard was found (data unavailable). This analysis suggests that citalopram may not increase the risk of VA/SD compared to paroxetine’s baseline incidence rate of 3.15 (95% CI, 2.93 to 3.38) cases per 1000 patient years.

**Conclusion**

The available studies provide inconclusive data to suggest that either citalopram or escitalopram is more likely to cause fatal arrhythmias due to QTc prolongation. There is a lack of head-to-head trials comparing these agent’s potential to cause QTc associated mortality at therapeutic doses.

The FDA’s evidence favors low doses of both citalopram and escitalopram as both agents showed dose related QTc prolongation.<sup>5</sup> Citalopram (20 mg/day) and escitalopram (10 mg/day) may theoretically increase the QTc interval by between 30 to 40 msec in 1 of 40 patients, and therefore put those with underlying factors at risk of arrhythmias or sudden death.

Contrasting the FDA’s findings, studies by Hanash et al.<sup>27</sup> and Lesperance et al.<sup>23</sup> found neither escitalopram 10 mg/day nor citalopram 20-40 mg/day lengthened the QTc interval in patients at increased risk of arrhythmias due to heart disease. Similarly, Leonard et al.<sup>24</sup> suggest that exposure to citalopram carries no greater risk of VA/SD compared to paroxetine, an antidepressant with a low propensity for QTc prolongation.

Considering the lack of evidence to suggest escitalopram has a safer cardiovascular profile than citalopram, a reasonable approach could be to consider citalopram

20 mg/day as a safe and effective option. Based on the FDA's assessment, 20 mg/day instead of 40 mg/day is a prudent recommendation due to the dose related effect on the QTc interval. While not contraindicated, the tolerability and efficacy of escitalopram is unknown and the increased cost of therapy may compromise adherence and persistence with antidepressant therapy. Physicians should regularly screen for QTc prolonging risk factors and strongly consider an ECG at baseline and after six months of therapy. In addition to counselling and antidepressant therapy, patients should be advised to promptly report dizziness, palpitations, or syncope, as these symptoms may be indicative of cardiovascular conduction abnormalities.<sup>5</sup>

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