

## FAQ Citalopram, Escitalopram and QTc prolongation

### ***What information has changed?***

The FDA recently issued a Drug Safety Communication cautioning healthcare practitioners and patients that the antidepressant Celexa®, citalopram hydrobromide, can cause a prolonged QT interval corrected for heart rate (QTc). The warning went on to state citalopram should no longer be used at doses greater than 40 mg per day. For patients over 60 years old, those with liver impairment, poor CYP 2C19 metabolizers or those on cimetidine, the maximum recommended dose is 20mg per day. Although the drug label change only involves citalopram at this time, clinical studies demonstrate caution is warranted with escitalopram as well.

### ***Why is a prolonged QTc important?***

Prolongation of the QT interval on the electrocardiogram (ECG) reflects an abnormal change in the electrical activity of the heart that can increase the risk of a fatal heart rhythm known as Torsade de Pointes. An analysis of the Rotterdam Study found that as the QTc interval increased, so did the risk of sudden cardiac death in adults by approximately 60%, independent of other risk factors.<sup>1</sup>

### ***How does citalopram compare to other drugs that prolong QTc?***

The new FDA warning was based on a study assessing citalopram dosing on the QT interval in adults. In this randomized, multi-center, double-blind, placebo-controlled crossover study, 119 subjects received citalopram 20mg per day on Day 9, citalopram 60mg per day on Day 22 and placebo with the following summary findings noted in table 1 below.

Table 1: Increase in the Corrected QT Interval for Citalopram (FDA Analysis)

<b>Citalopram Dose</b>	<b>Increase in QT Interval (ms)</b>	<b>90% Confidence Interval (ms)</b>
20 mg/day	8.5	(6.2, 10.8)
40 mg/day	12.6*	(10.9, 14.3)*
60 mg/day	18.5	(16.0, 21.0)

\*Estimate based on the relationship between citalopram blood concentration and QT interval.

Upon reviewing these QT results, along with citalopram data measuring dose response, the FDA no longer recommends doses above 40mg per day. Of note, there was only one 6-week study performed that was applicable to measuring citalopram dose response. Since that study did not demonstrate an advantage of 60 mg per day versus 40mg per day, this contributed to the dose change language in the labeling.

### ***At what QTc interval should I start having concern?***

Studies are mixed and there is a lack of consensus as to what level of QT prolongation is clinically significant.<sup>2</sup> The risk of sudden cardiac death is affected by more than the corrected QT interval and is also impacted by gender and the patient's genotype for the disorder, but the highest risk is typically associated with QTc greater than 500 msec.<sup>3</sup>

### ***What other factors increase the risk?***

Citalopram and escitalopram should not be used in patients with congenital long QT syndrome. Individuals at greater risk for QT interval prolongation and Torsade de Pointes warrant additional monitoring.

- Caution and more frequent ECG monitoring may be necessary for:
  - Underlying heart conditions including CHF, bradyarrhythmias, history of myocardial infarction, hypertrophic cardiomyopathy

- Concurrent use with other medications that prolong QTc (<http://www.qtdrugs.org>)
- Concurrent use of CYP3A4 enzyme inhibitors (<http://medicine.iupui.edu/clinpharm/ddis/table.aspx>)
- Caution and correction of electrolyte disturbances in advance and more frequent monitoring of electrolytes for patients on diuretics or those with diarrhea or vomiting who may have:
  - Hypokalemia
  - Hypomagnesemia

### **What other medications prolong the QT interval?**

Other medications shown to prolong the QT interval and increase the risk of Torsade de Pointes and sudden death include antiarrhythmic drugs (e.g. amiodarone, sotalol, disopyramide, procainamide), macrolide antibiotics (e.g. erythromycin, clarithromycin, azithromycin), antifungals (e.g. ketoconazole, fluconazole, itraconazole), antimalarials (chloroquine), TCAs (amitriptyline, imipramine, doxepin), antipsychotics (thioridazine, ziprasidone/Geodon<sup>®</sup>, haloperidol), prokinetics (cisapride) and antiemetic medications (ondansetron/Zofran<sup>®</sup>, granisetron/Kytril<sup>®</sup>). For a more complete list of medications, please go to <http://www.qtdrugs.org>

### **What signs and risk factors should I look for when assessing patients?**

- Heart disease, history of unexplained cardiac arrest, fainting or seizures.
- Complaints of lightheadedness, dizziness, palpitations or transient breathlessness.
- A pulse less than 50
- Family history of long QT syndrome or sudden death before age 40
- Low potassium or magnesium

### **Recommendations**

1. The benefit and risks of all medications should be weighed with informed clinical decisions made for each individual patient.
2. Coordinate with the PCP to provide a baseline EKG if risk factors are present and/or a subsequent EKG if the patient has symptoms associated with QT interval prolongation such as syncope.
3. Avoid using citalopram in doses above 40 mg/day or escitalopram (Lexapro<sup>®</sup>) in doses above 20 mg/day.
4. Avoid using citalopram or escitalopram in recipients on thioridazine, mesoridazine or pimozide and use caution with concurrent use of citalopram or escitalopram with ziprasidone (Geodon<sup>®</sup>) or iloperidone (Fanapt<sup>®</sup>).

#### References:

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