UPDATE: CITALOPRAM HYDROBROMIDE (CELEXA®) AND DOSE-DEPENDENT QT INTERVAL PROLONGATION

I. ISSUE:
Post-marketing reports of QT interval prolongation and Torsades de Pointes associated with CELEXA® and its generic equivalents (citalopram) resulted in changes to the product labeling in August 2011. The Food and Drug Administration (FDA) announced further labeling changes on March 28, 2012.

II. BACKGROUND:
In August 2011, PBM issued a National PBM Bulletin addressing citalopram’s labeling revisions. These resulted from findings that citalopram has the potential for abnormal changes in the electrical activity of the heart when used in doses greater than 40mg per day. Information included new FDA dosing recommendations (i.e., dose reductions) and FDA monitoring parameters.

In September 2011, PBM released an updated National PBM Bulletin expressing additional guidance (per internal discussions among PBM, VAMedSAFE, Office of Mental Health Services, and the Office of the National Director of Cardiology) on the use of higher doses of citalopram than recommended in the product labeling, as well as periodic electrocardiogram (ECG) monitoring, in patients already maintained on higher doses or future patients whose benefits outweigh the risk of harm.

As of March 28, 2012, new changes have been made to the citalopram product label, specifically:
- ECG and/or electrolyte monitoring should be performed in patients prescribed citalopram who have relative contraindications to citalopram use, such as in those with comorbid conditions predisposing a risk of QT prolongation;
- Previous label recommendations that “contraindicated” citalopram use in patients with congenital QT syndrome because of the risk for QT prolongation have been changed to less stringent terminology of “not recommended” to recognize patients with this condition who could benefit from citalopram or who cannot tolerate other alternatives;
- The maximum dose of citalopram remains at 20mg/day for patients greater than the age of 60 years;
- Citalopram should be discontinued in patients with QTc measurements persistently above 500ms.

III. DISCUSSION:
FDA review of randomized, double-blind, placebo-controlled crossover studies looking at the effect of multiple doses of citalopram (CELEXA®) and its s-enantiomer escitalopram (LEXAPRO®) on QT-interval length in adults compared to moxifloxacin 400mg/day showed:
- Citalopram causes dose-dependent and clinically significant QT-interval prolongation with the 60mg daily dose;
- Citalopram does not have additional effectiveness at doses over 40mg daily.

See Table 1 for updated results reported by the FDA.

<table>
<thead>
<tr>
<th>CITALOPRAM DOSE [mg/day]</th>
<th>CITALOPRAM CHANGE IN QTc (90% CI) [ms]</th>
<th>ESCITALOPRAM DOSE [mg/day]</th>
<th>ESCITALOPRAM CHANGE IN QTc (90% CI) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>8.5 (6.2, 10.8)</td>
<td>10</td>
<td>4.5 (2.5, 6.4)</td>
</tr>
<tr>
<td>40</td>
<td>12.6 (10.9, 14.3)</td>
<td>20</td>
<td>6.6 (5.3, 7.9)</td>
</tr>
<tr>
<td>60</td>
<td>18.5 (16.0, 21.0)</td>
<td>30</td>
<td>10.7 (8.7, 12.7)</td>
</tr>
<tr>
<td>MOXIFLOXACIN 400mg/day</td>
<td>13.4 (10.9, 15.9)</td>
<td>MOXIFLOXACIN 400mg/day</td>
<td>9.0 (7.3, 10.8)</td>
</tr>
</tbody>
</table>

1Changes in QTc for citalopram 40 mg and escitalopram 20 mg are predicted based upon changes demonstrated with citalopram 10 mg and 60 mg and escitalopram 10 and 30 mg.

A search in the VA Adverse Drug Event Reporting System (VA ADERS) showed the following outcomes reported within the VA system-wide:
IV. PROVIDER RECOMMENDATIONS:
REVISED FDA RECOMMENDATIONS include:
- Citalopram may cause dose-dependent QT-prolongation, Torsades de Pointes, ventricular tachycardia, or sudden death.
- Citalopram is not recommended in patients with:
  - Congenital long QT syndrome;
  - Bradycardia;
  - Hypokalemia;
  - Hypomagnesemia;
  - Recent acute myocardial infarction;
  - Uncompensated heart failure;
  - Concomitant use of drugs that prolong the QT interval.
- Limit citalopram dose to a maximum of 20mg per day for patients with risk factors that may increase citalopram levels and risk of conduction abnormalities. The FDA has specifically warned about the following risks:
  - Age greater than 60 years;
  - Impaired CYP 2C19 metabolism;
  - Concomitant use of cimetidine or other CYP2C19 inhibitor agents;
  - Hepatic insufficiency.
- Perform ECG monitoring in patients initiating or maintained on citalopram but who have relative contraindications as mentioned above.
  - Discontinue citalopram in patients with QTc intervals greater than 500ms.
- In patients at risk for significant electrolyte disturbances, measure baseline potassium and magnesium levels. Correct hypokalemia and/or hypomagnesemia before initiation of citalopram therapy and monitor periodically while maintained on citalopram to ensure levels remain within normal limits.
- Educate patients on the signs and symptoms of abnormal heart rate/rhythm (dizziness, palpitations, syncope) and to notify their provider if they experience any of these symptoms.

VA-SPECIFIC RECOMMENDATIONS previously issued by PBM, VAMedSAFE, Office of Mental Health Services, and the Office of the National Director of Cardiology still applies as follows:
1. When possible, providers should refrain from prescribing citalopram in doses that exceed those in its label.
2. When possible, providers should attempt to reduce doses in patients whose current dose exceeds that in its label to those within its labeling.
3. VHA does recognize some patients require higher doses (off-label) of citalopram. In these cases the following should be observed:
   a. The provider has decided that the benefits outweigh the risk of harm (QTc prolongation, Torsade de Pointes) and has discussed this with the patient or caregiver.
   b. The above (a) has been documented in CPRS by the provider. (a and b apply to current and future patients.)
   c. For patients already on higher (off-label) doses of citalopram, an ECG will be done to document that the QTc is less than 500 msec. Prior to increasing citalopram to higher off-label doses, an ECG has been obtained and read prior to initiating the higher dose of citalopram. (An ECG obtained within the previous 3 months is acceptable.)
d. For future patients, an ECG is to be obtained and read prior to initiating the higher dose of citalopram. (An ECG obtained within the previous 3 months is acceptable.)

e. Serum potassium and magnesium concentrations have been obtained and abnormal concentrations corrected prior to initiating the higher dose of citalopram.

f. That periodic ECG and labs will be obtained during the course of therapy and prior to any additional dose increases.

g. If at any time the patient’s QTc is greater than 500 msec or if other risk factors for QTc prolongation are present (e.g., another drug that prolongs QTc is required), the dose will be reduced or citalopram will be discontinued.

h. The patient’s need for a higher dose should be assessed periodically and consider dose a reduction if appropriate.

4. Providers are to report adverse events to the VA’s adverse drug event reporting surveillance system (VA ADERS). VISN Mental Health leads are responsible for implementation and monitoring of this guidance within their VISNs.

V. REFERENCES:


2. Celexa® (Citalopram) [package insert]. St. Louis, MO: Forest Pharmaceuticals; August 2011.

**ACTIONS**

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).

- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers who handle these medications (e.g., primary care providers, mental and behavioral health providers, and clinic staff, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.

- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).