POTENTIAL FOR QT/QTc PROLONGATION WITH NON-SSRI ANTIDEPRESSANTS

QT prolongation is an important risk factor for sudden cardiac death. Although drug manufacturers must perform evaluations of the potential for QT prolongation with new agents, the potential for torsades de pointes (TdP) and cardiac death are top reasons that prompt the FDA from removing drugs from the US market. The FDA issued warnings about citalopram (Celexa) and the potential for QT prolongation in doses exceeding 40 mg; however, the risk of QT prolongation with non-SSRI antidepressants has not been fully elucidated. This issue of CLIPS briefly summarizes a literature review on the potential for QT prolongation with newer non-SSRI antidepressants. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Background

- QTc (corrected QT) is a corrected value of heart rate using specific calculations (e.g., Bazett’s or Fridericia’s formulas).
- Risk factors for QT prolongation include: female gender, select cardiac abnormalities (e.g., dilated cardiomyopathy), and electrolyte imbalances (e.g., hypokalemia, hypomagnesemia).
- The risk of torsades de pointes (TdP) increases when QT > 20 ms from baseline; however, many clinicians use a cut off of a QT increase of 60 ms from baseline or a QT interval above 500 ms as a clinical indicator for discontinuing medications.
- A recent FDA warning regarding QTc prolongation with citalopram (Celexa) prompted the manufacturer to issue new dosage guidelines.
- Approximately 10% of the US population has taken an antidepressant in the past 30 days, as reflected from 2007-2010 data.
- Increases in antidepressant use are speculated due to the variety of clinical conditions for which they are prescribed.

Methods

- A PubMed search was performed to determine the association of non-SSRI agents (e.g., bupropion, desvenlafaxine, duloxetine, levomilnacipran, mirtazapine, venlafaxine, and vilazodone) with QTc prolongation.
- Manufacturer information and a list of QT prolonging drugs on the ArizonaCert website were consulted.

Bupropion

- Electrocardiogram (ECG) abnormalities are listed in the package insert as an adverse effect in overdoses.
- Most of the information presented comes from overdose situations; however, one investigator evaluated the effects of bupropion cardiotoxicity in a double-blind, clinical trial.
- In three older studies, doses of bupropion (100-200 mg) were associated with an inverse relationship with QTc intervals. As the dosage of bupropion increased, the QTc decreased.
- In the double-blind trial, bupropion dosage exceeded the maximum dose (mean dose, 552 mg; maximum dose, 750 mg) and no QTc interval changes were observed.
- Bupropion’s potential for QT prolongation may be increased in overdose situations and/or when bupropion is administered concomitantly with other QT-prolonging medications. Therapeutic doses of bupropion do not appear to prolong QT intervals.

Desvenlafaxine

- No articles were located describing the effects of desvenlafaxine on QT interval prolongation. Information from the manufacturer was used instead.

CONTINUED NEXT PAGE
Desvenlafaxine (continued)
- Premarketing reports of QTc prolongation were not significantly different between desvenlafaxine-treated patients (n=1492) and placebo (n=984)
- Desvenlafaxine does not appear to prolong QT interval.

Duloxetine
- In a review of duloxetine, therapeutic doses revealed a non-clinically significant decrease in QT interval in patient receiving duloxetine.
- In a randomized, double-blind, placebo-controlled, cross-over study, duloxetine doses of 60-200 mg twice daily) were not associated with a significant difference in QTc between duloxetine and placebo.

Levomilnacipran
- No published literature was found regarding levomilnacipran and QT prolongation.
- No information was provided from the manufacturer for QT prolongation potential.

Mirtazapine
- Reports from the manufacturer indicate that QT prolongation has occurred in patients receiving mirtazapine; however, details from the case reports were not provided.
- Mean increases in QTc with mirtazapine was 1.6 ms compared with placebo. QTc interval did not exceed 500 ms.
- Information with mirtazapine overdoses does not indicate QT changes. A Medicaid claims data report indicated a significantly greater risk of sudden death and ventricular arrhythmias with mirtazapine compared to paroxetine (HR, 1.26; 95 % CI, 1.11-1.42).
- The risk of QT prolongation with mirtazapine is minimal. ArizonaCert lists mirtazapine as a QT-prolonging drug.

Venlafaxine
- Venlafaxine has the most information available related to QT prolongation. ArizonaCert lists venlafaxine as a QT-prolonging drug.
- Correspondence from the manufacturer revealed a mean increase in QTc from baseline in patients treated with venlafaxine XR (n=275) for major depressive disorder was 4.7 ms vs 1.9 ms in patients receiving placebo (n=220). Results from studies in patients with seasonal affective disorder (SAD) revealed a QT interval increase of 3.4 ms in patients (n=593) receiving venlafaxine XR and a 1.6 ms decrease in patients (n=534) receiving placebo.
- Case reports documenting QT interval changes occurred in patients receiving therapeutic doses and overdoses.
- In summary, QT prolongation is more likely to occur in overdose situations, but can occur at therapeutic doses in elderly patients.

Vilazodone
- A PubMed search revealed no literature regarding QT prolongation changes with vilazodone.
- Additional information from the manufacturer revealed no clinically significant increases in QT prolongation.

Conclusion
- Risk factors for QT prolongation should be evaluated when patients receive a medication that may prolong QT interval.
- Data suggest that mirtazapine, desvenlafaxine, duloxetine, levomilnacipran, and vilazodone do not increase QT prolongation. However, ArizonaCert lists mirtazapine as a QT-prolonging drug.
- Bupropion and venlafaxine have the greatest risk of QT prolongation, especially in overdose situations.

Prepared by: Maisha Kelly Freeman, Pharm.D.,MS, BCPS, FASCP