RISK OF QTC PROLONGATION AND TORSADES DE POINTES WITH CITALOPRAM, ESCITALOPRAM AND TRAZODONE IN GERIATRIC PATIENTS

By: Gabrielle Crépeau-Gendron, MD, FRCPC
Candidate for Geriatric Psychiatrist title

Co-researchers:
Hilary K. Brown
Robert Madan
Claudia Szabuniewicz, Samantha Koh
Shelley Veinish, Altaf Kassam

Research supervisor : Dr Linda Mah
Presenter Disclosure

• This study has received financial support from Baycrest Health Science – Academic Development Fund.

• Potential for conflict(s) of interest:
  – Nothing to declare

• Relationships with commercial interests:
  – None
Plan

1. The clinical dilemma with the Health Canada warning with citalopram and escitalopram

2. The research project

3. The impact on our clinical practice
Learning objectives

• To be able to list 5 risk factors for QTc interval prolongation and 3 common drugs associated with QTc prolongation.

• To develop a safe approach to optimal psychotropic medication prescribing in the case of QTc prolongation.
HEALTH CANADA WARNING - 2012

- Citalopram **20 mg** and escitalopram **10 mg** per day are the **maximum** recommended dose for patients:
  - With hepatic impairment
  - **Who are 65 years of age or older**
  - Who are CYP2C19 poor metabolizers
  - Who are taking concomitant cimetidine or another CYP2C19 inhibitor.
WHY USE CITALOPRAM?

• Well studied
  – Up to 30 mg for BPSD (Porsteinsson et al, 2014)
  – Many studies in heart disease (CREATE trial, 2007)

• Well tolerated
  – Few side effects
  – Few drug interactions

• Sometimes higher doses needed (e.g. anxiety disorders, treatment resistant depression) vs adding other medication?
HEALTH CANADA WARNING IS NOT WITHOUT RISK

• Study Veterans USA 2016
• 35 848 patients
• Reduction of citalopram dosages in patients who had been treated with substantially higher doses than the new maximum recommended dose by FDA was associated with:
  – ↑ rate of all cause hospitalizations
  – ↑ rate of depression related hospitalizations
THE DILEMMA FOR CLINICIANS

• For patients already on citalopram/escitalopram high dose
  – Risk relapse and complications that ensue (morbidity, hospital admission, etc.)
  – Vs risk malpractice litigation?

• For new patients
  – Avoid effective and well tolerated medication?
  – If partial response, add-on therapy more quickly → polypharmacy?
    • Antipsychotics and lithium also increase QTc...
TORSADES DE POINTES: the real worry

• Form of polymorphic ventricular tachycardia that occurs in the setting of QTc interval prolongation
• Usually short-lived and terminate spontaneously but can recur!
  – Often asymptomatic!
  – Palpitations
  – Syncope (most common)
  – Seizures
• May evolve to ventricular fibrillation and sudden cardiac death

• Incidence is low among general clinical populations (Hennessy et al. 2002 and Enger et al. 2002)
QTc INTERVAL

- Normal: ♂ < 450 ms  ♀ < 470 ms

- The risk of TdP increases as the QTc interval increases, particularly > 500 ms (Moss et al. 1991, Woosley et al. 1993)

- Only a small portion of patients that develop drug-induced QTc interval prolongation experience TdP.

- There is no threshold of QTc prolongation at which TdP is certain to occur.
Risk factors for prolonged QT - ACQUIRED

- Female gender
- Advanced age
- Certain drugs
- Hypothyroidism
- Electrolyte imbalance
  - Hypokalemia, hypomagnesemia and hypocalcemia (K, Mg, Ca)
- Cardiac abnormalities
  - Heart failure, myocardial infarction, left ventricular hypertrophy
- Anorexia / malnutrition
- Bradyarrhythmias
  - Sinus node dysfunction
  - Atrioventricular (AV) block – second- or third-degree
RISK FACTORS FOR ↑ QTc

• Many drugs can increase QTc
• **Antibiotics** (-mycin, -floxacin), **Antipsychotics**, **Antidepressants** (tricyclics, mirtazapine, paroxetine, sertraline.....)
• **Antiarrythmics** (amiodarone, sotalol...)
• [https://www.crediblemeds.org/](https://www.crediblemeds.org/)
OUR STUDY - context

• Recently, 2 studies examined the relationship between antidepressants and QTc interval based on electronic medical record data (adult and pediatric populations).

• Secondary analyses of a study in patients with dementia (CiTAD, Porteinsson et al., 2014) found an increase in QTc of 18.1 ms with citalopram 30 mg compared to placebo (N = 44 including patients on placebo)

• **OBJECTIVE**: to assess the association between citalopram, escitalopram and QTc interval, torsades de pointes (TdP), and sudden cardiac death in older adults.

• We used trazodone as a comparison group:
  – Considered to have low risk of QTc prolongation and is only associated with TdP when in combination with other risk factors (e.g., hypokalemia, drug interactions)
OUR STUDY - methods

• We conducted a retrospective cohort study.

• **Electronic health records:**
  – Baycrest Health Sciences, April 2008 to July 2015
  – Patients on citalopram, escitalopram, or trazodone
  – Who had an electrocardiogram (EKG) within 90 days following the initiation or dosage change of these medications.

• Charts were reviewed for:
  – **Reports of TdP or sudden cardiac death**
  – Other risk factors for prolongation of QTc interval such as cardiac conditions and medications.

• We used linear regression to examine the impact of the medications on the outcomes for each of the target drugs of interest. Exposure variables were:
  1. Drug dosage as a continuous variable and
  2. Doses above vs. below the maximum recommended dose by Health Canada.
OUR STUDY - methods

A power analysis showed the need for 50 to 116 patients to identify a difference in QTc of 5 ms.

5ms = threshold level of regulatory concern for FDA (upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms)

• Source: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (FDA, 2005)
OUR STUDY – preliminary results

Baseline characteristics of study sample

- Mean age = 82 years old
- Drug of interest
  - Citalopram = 106 patients
  - Escitalopram = 46 patients
  - Trazodone = 101 patients
- Female gender : 58%
- Setting: inpatient, rehab, long term care
  - Only 2% outpatients
- Heart disease : 49%
- Severe renal failure: 20%
- Electrolyte abnormalities: 7%
- No dementia = 32% (and 10% unclear diagnosis)
Table 2. Association between antidepressant dose and QTc interval

Description of analysis: Linear regression. Outcome is QTc interval as a continuous variable; independent variables are antidepressant dose as continuous variables.

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Unadjusted β (p-value)</th>
<th>Adjusted β (p-value) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>-0.158 (p = 0.675)</td>
<td>-0.062 (p = 0.880)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0.305 (p = 0.728)</td>
<td>0.922 (p = 0.326)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>-0.009 (p = 0.872)</td>
<td>0.027 (p = 0.681)</td>
</tr>
</tbody>
</table>

*Adjusted β controls for: age, female gender, heart disease, severe renal failure, electrolyte abnormalities, psychotropic medications, non-psychotropic medications
Table 3. Association between antidepressant dose (above vs. below recommended threshold) and QTc interval

Description of analysis: Linear regression. Outcome is QTc interval as a continuous variable; independent variables are antidepressant dose thresholds as binary variables (above vs. below threshold).

<table>
<thead>
<tr>
<th>Description of Analysis</th>
<th>Unadjusted β (p-value)</th>
<th>Adjusted β (p-value) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram &gt;20 mg/day (N= 33, total sample = 106)</td>
<td>-6.860 (p = 0.393)</td>
<td>-6.032 (p = 0.478)</td>
</tr>
<tr>
<td>Escitalopram &gt;10 mg/day (N= 18, total sample = 46)</td>
<td>-3.682 (p = 0.727)</td>
<td>8.362 (p = 0.477)</td>
</tr>
<tr>
<td>Trazodone ≥100 mg/day (N= 35, total sample = 101)</td>
<td>3.240 (p = 0.666)</td>
<td>5.645 (p = 0.509)</td>
</tr>
</tbody>
</table>

*Adjusted β controls for: age, female gender, heart disease, severe renal failure, electrolyte abnormalities, psychotropic medications, non-psychotropic medications.
OUR STUDY - preliminary results

Figure 1. Box and whisker plot of QTc by medication type showing median, interquartile range and minimum and maximum QTc values by antidepressant type.
OUR STUDY - preliminary results

4 reports of sudden cardiac death:
- 1 in citalopram group (QTc was 467 ms in study)
- 1 in escitalopram group (QTc was 418 ms)
- 2 in trazodone group (QTc were 436 ms and 442 ms)
OUR STUDY - conclusion

• We did not find an association with citalopram, escitalopram and trazodone and an increased QTc interval

• Why is it different?
  – Other studies with same findings in past (Rasmussen et al., 1999, Retrospective: more than 6,000 ECGs (N = 1,789 citalopram-treated patients – 5 to 60 mg daily) (CREATE trial, 2007)
  – Older population: so many risk factors that citalopram does not have major impact?
  – Decrease in dosages of citalopram after 2012?
    • Add analysis comparing BEFORE AND AFTER warning

• Unfortunately, not enough subjects had ECG BEFORE drug initiation so we cannot comment on change in QTc within the same patient.
HOW TO PRESCRIBE SAFELY

• If available, I would recommend a baseline ECG in our geriatric population before starting an antidepressant such as citalopram and escitalopram, especially if other risk factors
  – Age is important risk factor for QTc prolongation
  – More polypharmacy
  – Need for a baseline to know if medication had impact...
  – Could influence choice of antidepressant
  – Could avoid discontinuation of effective medication!
HOW TO PRESCRIBE SAFELY

• If prolonged:
  – Lab work: TSH, lytes, Ca, Mg
  – Correct abnormalities
  – Review meds and discontinue
    • Domperidone, oxybutinine, antipsychotics, furosemide...

• Good opportunity for meds review!

• Ideally get follow up ECG after dose changes or adding other QTc prolonging medication
KEY POINTS TO REMEMBER

• Decision can be individualized for each patient:
  – Other risk factors
  – ECG monitoring
  – Risks vs benefits of using citalopram or escitalopram vs other antidepressants
    • most have a risk of TdP, although possibly lower
  – Concomittant drugs

• Impact on QTc may not be as important as the warnings suggest...
THANK YOU

Questions?

gabriellecg25@hotmail.com
## OUR STUDY – preliminary results

### Table 1. Baseline characteristics of study sample

<table>
<thead>
<tr>
<th></th>
<th>Antidepressant users with EKG (N= 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>82 (9.22)</td>
</tr>
<tr>
<td>Drug of interest (citalopram, escitalopram, trazodone)</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>106 (41.90%)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>46 (18.18%)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>101 (39.92%)</td>
</tr>
<tr>
<td>Female gender</td>
<td>146 (57.7%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Inpatient, medical</td>
<td>30 (11.9%)</td>
</tr>
<tr>
<td>Inpatient, psychiatry</td>
<td>32 (12.7%)</td>
</tr>
<tr>
<td>Long-term care</td>
<td>94 (37.5%)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>5 (1.98%)</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>46 (18.2%)</td>
</tr>
<tr>
<td>Behavioural neurology unit</td>
<td>46 (18.2%)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>124 (49.0%)</td>
</tr>
<tr>
<td>Coronary artery disease or Left ventricular hypertrophy</td>
<td>103 (40.7%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>48 (19.0%)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>44 (17.4%)</td>
</tr>
<tr>
<td>Severe renal failure (creatinine clearance &lt; 30 ml/min)</td>
<td>50 (19.8%)</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>18 (7.1%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>11 (4.4%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4 (1.6%)</td>
</tr>
</tbody>
</table>
Table 1. Baseline characteristics of study sample

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td>No dementia</td>
<td>80 (31.6%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>148 (58.5%)</td>
</tr>
<tr>
<td>Diagnosis unclear</td>
<td>25 (9.9%)</td>
</tr>
<tr>
<td>Psychotropic medications</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>46 (18.2%)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>89 (35.2%)</td>
</tr>
<tr>
<td>Lithium</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>Cholinesterase inhibitors (Donepezil, Galantamine)</td>
<td>53 (21.0%)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>132 (52.2%)</td>
</tr>
<tr>
<td>Trazodone PRN</td>
<td>50 (19.8%)</td>
</tr>
<tr>
<td>Antipsychotics PRN</td>
<td>22 (8.7%)</td>
</tr>
<tr>
<td>Other medications prolonging QTc interval</td>
<td>152 (60.1%)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs</td>
<td>22 (11.1%)</td>
</tr>
<tr>
<td>Anti-infectious (antibiotics, antimalarials, antifungals)</td>
<td>22 (8.7%)</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>24 (9.5%)</td>
</tr>
<tr>
<td>Bronchodilators PRN</td>
<td>27 (10.7%)</td>
</tr>
<tr>
<td>GI drugs (pantoprazole, domperidone)</td>
<td>77 (30.4%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>78 (30.8%)</td>
</tr>
<tr>
<td>Other QTc prolonging medications (antihistamines, tamoxifen, tolterodine…)</td>
<td>12 (4.7%)</td>
</tr>
<tr>
<td>Indication for Citalopram / Escitalopram / Trazodone</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>71 (28.1%)</td>
</tr>
<tr>
<td>Behavioural and psychological symptoms of dementia</td>
<td>106 (41.9%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (3.6%)</td>
</tr>
<tr>
<td>Bipolar depression</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Insomnia unexplained by other psychiatric condition</td>
<td>43 (16.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (2.4%)</td>
</tr>
</tbody>
</table>