Citalopram and escitalopram: adverse cardiac outcomes in medically ill inpatients

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Serotonin selective reuptake inhibitors (SSRIs) have widely replaced older tricyclic antidepressants (TCAs) in the treatment of depression and anxiety over the years, given their safer cardiac profile [Glassman, 1998]. Even at therapeutic doses, TCAs commonly cause a slowing of intra-ventricular conduction through their sodium-channel blocking properties, leading to prolonged PR, QRS and QT intervals [Pacher and Kecskemeti, 2004]. Similarly, *in vitro* and animal studies have shown that citalopram and escitalopram, through their cardiotoxic metabolite, didesmethylcitalopram, can delay ventricular repolarization, prolong QT, and increase the risk of *torsade de pointes* by directly blocking potassium-HERG channels in cardiomyocytes [Overa, 1989; Witchel *et al.* 2002]. In 2011–2012, the US Food and Drug Administration (FDA) released a safety communication regarding citalopram and escitalopram and their increased risk for QTc prolongation and cardiac outcomes, especially in elderly and patients with comorbid medical illnesses [FDA, 2012]. The new FDA recommendations state that citalopram should not be used at doses greater than 40 mg per day in healthy adults, and not exceed 20 mg per day in the elderly, patients with hepatic impairment, or patients taking a CYP2C19 inhibitor. Health Canada released a similar warning for escitalopram in 2012, stating that doses greater than 10 mg should be avoided in these latter high-risk populations [Health Canada, 2012]. A retrospective cross-sectional study in elderly surgical patients published in 2014 showed no association between citalopram and escitalopram and cardiac outcomes in this vulnerable population [van Haelst *et al.* 2014]. However, this association has never been assessed in a sample of acutely medically ill inpatients, another highly vulnerable population.

We performed a retrospective cohort study, including 275 medically ill inpatients, randomly

selected out of 923 patients assessed by the psychiatric consultation–liaison (C–L) team for anxiety or depressive symptoms between 2008 and 2014 at the Jewish General Hospital (JGH) in Montreal, Canada. Patients were followed from the date they were first assessed by the C–L team to a maximum of 30 days. They were divided into three exposure groups based on their current use of antidepressants (ADs): (1) citalopram/escitalopram (C/E), (2) other ADs, or (3) no ADs (non-ADs). We analyzed the association between AD exposure, adverse cardiac outcomes (ventricular arrhythmias and sudden cardiac deaths), and QTc prolongation (QTc $\geq$ 500 ms, or increase in QTc $\geq$ 60 ms). The JGH Research Ethics Committee approved this study.

Of the 275 medically ill inpatients, 89 (32.4%) were exposed to C/E, 74 (26.9%) to ADs, and 112 (40.7%) to non-ADs. The proportion of inpatients on citalopram less than 20 mg, citalopram 20–40 mg, citalopram more than 40 mg, and escitalopram 5–30 mg was 43.8%, 47.2%, 2.2% and 6.7%, respectively. Inpatients in the AD group were either exposed to venlafaxine XR (20.4%), sertraline (18.5%), paroxetine (14.8%), mirtazapine (11.1%), amitriptyline (9.6%), desvenlafaxine (7.4%), bupropion (7.4%), fluoxetine (5.6%), fluvoxamine (3.7%) or duloxetine (1.9%). Patients were aged 18–99 years (mean 60.9) and 60.6% were female. The mean number of medical comorbidities, medications, and concurrent QTc-prolonging medications per patient was 4.4, 10.1 and 0.5, respectively. None of the patients were admitted for medication overdose. Patients' mean baseline QTc ($n = 170$) was 434.0 ms, and mean length of stay in hospital was 41.5 days. The non-AD group was younger, had more females, took more nonpsychotropic medications, and had a better health profile (fewer medical comorbidities, QTc-prolonging medications, lower baseline QTc, and shorter length of stay) ($F > 3.86$, $p < 0.023$).

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No adverse cardiac outcomes were observed in the C/E group, comparable with results observed in the other groups (C/E 0% versus AD 0% versus non-AD 4.9%, $\chi^2(2) = 7.85$, $p = 0.02$, no significant *post hoc* Bonferroni pairwise differences). None of the patients developed *torsade de pointes*. The incidence of QTc prolongation (C/E 5.3% versus AD 5.3% versus non-AD 11.1%, $\chi^2(2) = 0.42$, $p = 0.81$), and the mean change in QTc (two EKGs available in $n = 47$) (C/E 2.48 ms versus AD 7.15 ms versus non-AD 7.89 ms, $F(2, 45) = 1.25$, $p = 0.30$) did not differ between groups. This remained the case in multivariate analyses controlling for age, gender, medical comorbidities, number of medications, number of QTc prolonging medications, baseline QTc, and length of stay. No differences were found between patients using C/E above recommended doses ($n = 8$) and other patients.

In this small sample of acutely medically ill inpatients exposed to C/E and other ADs, we did not find evidence of significant QTc prolongation or adverse cardiac outcomes. The observational nature of the data makes it impossible to identify a causal role of ADs in the QTc prolongation, as might better be compared using a before-and-after-treatment approach. The non-AD group differed from other groups with regards to certain clinical factors, making it a less-than-ideal comparator group, although we tried to control for this statistically. It seems reasonable for clinicians to cautiously use citalopram and escitalopram in this population, when the benefits outweigh the risks. However, clinicians should closely monitor for QTc prolongation in acute cases of citalopram overdose since its QT effects differ from other SSRIs in patients that take intentional drug overdose [Waring, 2010].

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