**Study Question**

What effects do antidepressants such as citalopram have on QT interval, a marker of risk for ventricular arrhythmia?

**Summary Answer**

In a large clinical cohort escalating doses of citalopram, escitalopram, and amitriptyline were significantly associated with prolonged QT interval, while bupropion was associated with shortened QT interval.

**What Is Known and What This Paper Adds**

The US Food and Drug Administration issued warnings about the QT prolonging effects of citalopram based on postmarketing surveillance and a small crossover study in healthy individuals. This study confirms a modest prolongation of QT interval with citalopram and identifies other antidepressants with similar observed risk in an older, more medically ill population.

**Participants and Setting**

The study included 38,397 adult patients in a large New England healthcare system who underwent electrocardiography after prescription of an antidepressant or methadone between February 1990 and August 2011.

**Design**

This cross-sectional study used electrocardiographic, prescribing, and clinical data drawn from electronic health records to explore the relation between antidepressant dose and corrected QT (QTc) interval. The present analysis included the selective serotonin reuptake inhibitor antidepressants citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; other antidepressants such as amitriptyline, nortriptyline, bupropion, duloxetine, mirtazapine, and venlafaxine; and the opioid methadone, known to prolong QT interval and included to demonstrate assay sensitivity.

**Primary Outcome(s)**

Relation between antidepressant dose and QTc interval was analysed by linear regression, with adjustment for potential clinical and demographic confounding variables.

**Main Results and the Role of Chance**

Dose-response association with QTc prolongation was identified for citalopram (adjusted beta 0.10 (SE 0.04), P<0.01), escitalopram (adjusted beta 0.58 (0.15), P<0.001), and amitriptyline (adjusted beta 0.11 (0.03), P<0.001), while an association with QTc shortening was identified for bupropion (adjusted beta 0.02 (0.01), P<0.05). The seven other antidepressants showed no significant effects. As expected, increasing methadone dose was also associated with increased QTc (adjusted beta 0.30 (0.06), P<0.001).

**Bias, Confounding, and Other Reasons for Caution**

Antidepressant type and dose were not randomly assigned, and electrocardiography was performed only when clinically indicated, which may introduce bias. However, as the data preceded the US Food and Drug Administration (FDA) warning about the QT-prolonging effects of citalopram, the risk for confounding by indication is low.

**Generalisability to Other Populations**

The concordance of our results with those of an FDA crossover study suggests their generalisability, though our results may be more relevant to an older, more medically ill population than that studied in the FDA trial.

**Study Funding/Potential Competing Interests**

The study was funded by the US National Institute of Mental Health.

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**Mean (SD) corrected QT (QTc) interval recorded on electrocardiogram 14–90 days after prescription of selective serotonin reuptake inhibitor antidepressant or methadone, by drug dose**

* Dose a significant predictor of QTc in fully adjusted linear models at α=0.05
† QTc at specified dose is significantly different from that at prior dose in fully adjusted linear models at α=0.05