The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Antidepressants and QTc prolongation

A family physician calls you seeking advice on a 58-year-old man with depression. He was treated with 60 mg/d of citalopram and is currently in remission with no side effects. However, the physician has just read the Health Canada warning on the risk of a corrected QT interval (QTc) prolongation with citalopram and the revised maximum recommended dose of 40 mg/d. She asks whether she should decrease the patient's dose.

There is considerable clinical confusion about the risks of QT prolongation with the use of antidepressants and psychotropics. The QT interval is an electrocardiographic (ECG) measure that varies with heart rate, hence a QTc is used. A QTc prolongation indicates delayed ventricular repolarization, which can trigger arrhythmias like Torsades de pointes (TdP; referring to the characteristic appearance of the ECG during the arrhythmia), a rare cardiac arrhythmia that can lead to syncope, seizures and sudden cardiac death.

In healthy individuals, the average QTc is about 400 ms; the upper limit of normal is considered to be 450 ms for men and 460 ms for women. A QTc longer than 500 ms[1–3] or an increase in QTc greater than 60 ms[4] is considered a major risk factor for TdP. Women are more likely to have increased sensitivity to drug-induced QTc prolongation and a higher risk of TdP. There are also genetic risk factors, such as congenital long QT syndrome, which affects 1 in 5000.[1] Other risk factors for QTc prolongation include structural heart disease, bradycardia, severely reduced renal function, hypokalemia, hypomagnesaemia and hypocalcaemia. It should be noted that QTc prolongation is only modestly associated with TdP, although it is the best predictor available.

Many psychotropic and nonpsychotropic medications carry risks for QTc prolongation. The Arizona Center for Education and Research on Therapeutics (AzCERT) keeps up-to-date information on drug-related QTc risks. The most established risks, with AzCERT ratings of 1 (generally accepted risk of TdP), include typical antipsychotics (chlorpromazine, haloperidol, pimozide) and methadone.[5] Citalopram has recently been added to that list, but no other antidepressants, including escitalopram, are in class 1. Even with the established class 1 risk drugs, only sporadic cases of TdP have been reported.[6]

The warning from Health Canada about citalopram resulted from postmarketing reports of TdP and a QTc study requested by the US Food and Drug Administration (FDA) involving healthy participants taking 20 mg and 60 mg doses of citalopram (Table 1). The 60 mg dose resulted in an average change in QTc of 18.5 ms and an upper bound of 21.0 ms, which was higher than the accepted range for risk. The interpolated QTc change for a 40 mg dose was 12.6 ms (upper bound 14.3 ms), which is within the acceptable range (and similar to that for lithium), hence the revised maximum dose of 40 mg/d. However, the QTc change on the 60 mg dose was still much lower than the 60 ms criterion that infers clear risk for TdP and lower than QTc changes found with other medications, including haloperidol, nortriptyline and ziprasidone. Several recent systematic reviews have suggested that the risks for TdP are very low with this magnitude of QTc prolongation.[6–8]

A related question is whether escitalopram, the S-enantiomer of citalopram, also carries the same risk. According to the data, it does not. A similar QTc study was done using 10 mg and 30 mg of escitalopram (Table 1). The 30 mg dose was within the acceptable range for QTc change (average 10.7 ms, upper bound 12.7 ms), and less than the interpolated result for the 40 mg dose of citalopram. Based on these data, the FDA did not request changes to the escitalopram monograph. Of note, a recent study of escitalopram in patients with depression and coronary artery disease did not find any significant changes in QTc.[9]

In summary, the effects of citalopram and other antidepressants in therapeutic doses on QTc are not likely to be of clinical relevance unless other known risk factors are present. The

Table 1: Dose-dependent change in corrected QT interval for citalopram and escitalopram*

Medication	Dose	Change in QTc (95% CI), ms
Citalopram	20 mg	8.5 (6.2–10.8)
	40 mg†	12.6 (10.9–14.3)
	60 mg	18.5 (16.0–21.0)
Escitalopram	10 mg	4.5 (2.5–6.4)
	20 mg†	6.6 (5.3–7.9)
	30 mg	10.7 (8.7–12.7)

CI = confidence interval; QTc = corrected QT interval.
*Revised Mar. 27, 2012, to include escitalopram.
†Estimate based on the relationship between blood concentrations and QT interval.
Source: www.fda.gov/drugs/drugsafety/ucm297391.htm (accessed 2012 Dec. 19).

Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 650 words long. Columns can include a bibliography which will be available only on the journal website.

patient in our scenario had no risk factors for QTc prolongation and was not taking any other QT-prolonging drugs, and an ECG showed a QTc of 420 ms. His depression only started improving after the dose increase to 60 mg. For these reasons, he could be maintained on the 60 mg/d dose. He should be carefully monitored if other drugs that affect QTc are added in future or if health conditions related to QTc prolongation develop.

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