

Escitalopram and QTc prolongation

One should not conclude from the discussion by Lam¹ that escitalopram is free of cardiac risks. Citalopram and escitalopram differ marginally in terms of their risk of prolonging the QTc interval sufficient to link to torsade de pointes (TdP). Citalopram and escitalopram each demonstrate a dose-dependent QTc prolongation.¹ Although the magnitude of QTc prolongation appears to be greater for citalopram than escitalopram, the dose-QTc correlation is similar for both drugs. While the U.S. Food and Drug Administration and Health Canada issued warnings only for citalopram, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom issued safety warnings for both citalopram and escitalopram.² The threshold for clinical significance of the QTc interval is an absolute duration of 500 ms or longer or a change from baseline of 60 ms or more.³ The warnings did not specify whether any participants enrolled in the thorough QTc studies exceeded these thresholds for either drug.

About 500 escitalopram overdoses and nearly 600 citalopram overdoses have been described, without serious cardiac sequelae or deaths due to either drug.⁴ Less than one-third of patients with citalopram overdoses presented with QTc interval prolongation. In 1 study, 14% of patients with escitalopram overdoses presented with QTc interval prolongation. In another study, the proportion of prolonged QTc intervals associated with escitalopram overdoses (1.7%) was not significantly different from that associated with citalopram overdoses (3.7%). These studies preclude a definitive assessment of the relative cardiotoxicity of citalopram versus escitalopram, but they do not demonstrate clinically meaningful differences in cardiotoxic effects.

The mechanisms underlying drug-associated QTc interval prolongation are not well understood. Drug dosage is only 1 of several factors that increase the

risk of QTc interval prolongation. In this regard it is notable that fewer than one-third of overdoses with citalopram or escitalopram are associated with QTc prolongation. If dose were a major factor with these drugs, you might expect that most overdoses would be associated with QTc prolongation. In our review,⁵ QTc interval prolongation or TdP due to citalopram occurred in the setting of citalopram overdose and/or in the presence of well-established risk factors, including advanced age, existing cardiac illness, multiple medical illnesses, electrolyte disturbances (hypokalemia, hypomagnesaemia) and concomitant use of QTc-prolonging drugs. These and other risk factors (baseline prolonged QTc, metabolic inhibition from other drugs, and hepatic impairment) have been emphasized in the regulatory warnings and would be particularly important for drugs like citalopram and escitalopram that prolong QTc interval marginally. Physicians should be mindful of these risk factors when prescribing these medications.

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Author response

Drs. Hasnain, Howland and Vieweg¹ have queried the issue of QTc risks of escitalopram versus citalopram. Of course, in a brief column it is difficult to pay justice to a complex topic, which is why I referenced some of their excellent publications on this topic. However, I note that they have previously raised the issue of an exaggerated regulatory response to the citalopram QTc data. In fact, the first conclusion in their comprehensive 2012 review in the *American Journal of Medicine* was, "Contrary to the assertions of the manufacturer of citalopram and the FDA [U.S. Food and Drug Administration] published in August 2011, we found no convincing evidence that citalopram, when used as prescribed in doses above 40 mg/day, was associated with an increased risk of QTc interval prolongation and torsade de pointes [TdP], as long as clinicians attended to well-known risk factors. And this drug at a 60 mg dose is no more likely to induce QTc interval prolongation than such drugs as ziprasidone and quetiapine."²

Given that Drs. Hasnain, Howland and Vieweg suggest that even citalopram has a low QTc risk, the question is not whether escitalopram has any risk, but rather how does that risk compare with that of other antidepressants and psychotropic medications, and how should clinicians deal with that risk? In this regard, they also note that, in contrast to Health Canada and the FDA, the Medicines and Healthcare Products