Escitalopram and QTc prolongation

One should not conclude from the discussion by Lam[1] 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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References

1. Lam RW. Antidepressants and QTc prolongation. *J Psychiatry Neurosci* 2013;38: E5-6.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Citalopram and escitalopram: QT interval prolongation — new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings. *Drug Safety Update* 2011;5:A1.
3. US Food and Drug Administration. (FDA). *Clinical Evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs*. Silver Spring, (MD): Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); 2005:E14.
4. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 1. *J Psychosoc Nurs Ment Health Serv* 2011; 49:13-6.
5. Vieweg WV, Hasnain M, Howland RH, et al. Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J Med* 2012;125:859-68.

Author response

Drs. Hasnain, Howland and Vieweg[1] 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

Regulatory Agency in the United Kingdom issued a safety warning for both citalopram and escitalopram. The fact that several regulatory agencies reached different conclusions based on essentially the same data set suggests that the issue is complex and subject to non-evidence-based opinions. In Europe, the regulatory warnings have also been criticized as exaggerated responses by several professional and scientific societies.[3,4] A pharmacovigilance study conducted by the Austrian Society of Drug Safety that included 57 911 patients treated with selective serotonin reuptake inhibitors (SSRIs; 16 351 with citalopram and 14 319 with escitalopram) in Austria, Germany and Switzerland found only 7 adverse cardiac events that were considered to be related to therapy with SSRIs (3 with sertraline and 1 each with citalopram, fluoxetine, fluvoxamine and paroxetine).[4] Only 2 cases of cardiac arrhythmia (1 with fluoxetine, 1 with sertraline), neither considered TdP, were identified. In this pharmacovigilance database, not a single case of escitalopram-induced adverse cardiac event was detected. Hence, there is little evidence of clinically significant adverse cardiac effects with escitalopram.

It is now recognized that there are often unintended consequences of regulatory agency warnings, as illustrated by the association with decline in diagnosis and treatment[5] and increase in suicide rates,[6] in the United States and Canada[7] following the regulatory warnings related to suicidality and antidepressants in children and youth. It is important that patients not be deprived of appropriate, effective and safe treatments based on premature and unsupported risk assessments.

While many antidepressants can have effects on QTc, the clinical relevance is still questionable. Certainly there is not enough evidence to change clinical practice for prescribing these medications, except for the usual caution of being aware of potential cardiac risks, particularly when patients have several non-drug-related risk factors for QTc prolongation and TdP. As Drs. Hasnain, Howland and Vieweg also noted in their review, "A large body of experience and data attest to the clinical effectiveness and cardiac safety of citalopram. Truncating its use at this time seems premature at best."[2] I would underscore that a therapeutic dose of escitalopram carries no greater cardiac risk than any other antidepressant and has a lower risk than other psychotropics, such as haloperidol, quetiapine and ziprasidone.

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References

1. Hasnain M, Howland RH, Vieweg WV. Escitalopram and QTc prolongation. *J Psychiatry Neurosci*. In press.
2. Vieweg WV, Hasnain M, Howland RH, et al. Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J Med* 2012;125:859-68.
3. Founder G, Aldenhoff JB, Bergmann F, et al. Statement of the German Society for Psychiatry, Psychotherapy and Neurology (DGPPN) on QTc interval prolongation under treatment with citalopram and escitalopram. *Stellungnahme* 2012;2. Available: http://www.dgppn.de/publikationen/stellungnahmen/detailansicht/browse/1/select/stellungnahmen-2012/article/141/zur-qtc-zeit.html
4. Haring C, Kasper S, Psota G. Opinion of the Austrian Society of Neuropsychopharmacology and Biological Psychiatry (ÖGPB) and the Austrian Society of Psychiatry and Psychotherapy (ÖGPP). Subject: Clinical relevance of the QTc interval prolongation associated with the use of citalopram and escitalopram. Vienna (DE): ÖGPB and ÖGPP; 2012 May 21.
5. Libby AM, Brent DA, Morrato EH, et al. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am J Psychiatry* 2007;164:884-91.
6. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007;164:1356-63.
7. Katz LY, Kozyrskyj AL, Prior HJ, et al. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. *CMAJ* 2008;178:1005-11.