See article by Ray et al

Caring for the Patient

James W. Jefferson, MD[a,*]

Almost 3 decades ago, the American Psychiatric Association published Task Force Report 27: "Sudden Death in Psychiatric Patients: The Role of Neuroleptic Drugs."[1] Among the issues discussed was psychotropic drug–associated cardiotoxicity and sudden death. QT interval prolongation and its relationship to the polymorphic ventricular tachycardia, torsade de pointes, was noted for both antipsychotics, especially thioridazine, and tricyclic antidepressants. These observations appeared just as the selective serotonin reuptake inhibitors (SSRIs) began their march to antidepressant dominance with the advent of fluoxetine in 1987 and, most recently, escitalopram in 2002.

In a safety announcement in 2011,[2] which was updated in 2012,[3] the US Food and Drug Administration (FDA) pointed an accusatory finger at citalopram, stating it carried a risk for causing QT interval prolongation at doses > 40 mg/d and that it should not be used at such doses. The FDA also discussed use of citalopram at any dose in patients with underlying heart disease and in those at risk for hypokalemia or hypomagnesemia. Lower doses (20 mg/d) were advised for patients > 60 years old. Furthermore, the recommendation for use in patients with congenital long QT syndrome was changed from "contraindicated" in 2011 to "not recommended" in 2012, acknowledging that there may be some circumstances in which low doses could be justified.

It should be noted that while long QT syndrome is often readily apparent on the electrocardiogram, there is also a subclinical (silent) variant in which QT interval is normal under basal conditions but which may become pathologically prolonged by acquired causes, including drugs.[4,5] Whether SSRIs as a group or individually increase this risk remains to be determined.

The citalopram story began in the 1980s, when toxicology studies in beagle dogs found QT interval prolongation and fatal arrhythmias.[6] These deaths were ascribed to high concentrations of didesmethylcitalopram, a toxic metabolite which, fortunately, was noted to be present in quite low concentrations in humans. Vieweg et al[7] muddied the safety waters a bit by pointing out that persons who are cytochrome P450 2D6 ultrarapid metabolizers could reach high concentrations of this cardiotoxic metabolite and actually be at increased risk for potentially lethal arrhythmias.

In 2004, Isbister et al[8] reported on the toxicity of SSRIs in overdose and found that QTc interval prolongation was greater with citalopram than with fluoxetine, fluvoxamine, paroxetine, or sertraline. They concluded that, except for citalopram, SSRIs are relatively safe in overdose.

Ten years later, Beach et al,[9] in a meta-analysis of SSRI-associated QTc prolongation, concluded that "citalopram was associated with more QTc prolongation than most other SSRIs."(p e441)

Not unexpectedly, a number of authors have risen to the defense of citalopram. In a 2-part article, Howland[10,11] critically evaluated the cardiac toxicity of citalopram and concluded, "Three studies comparing citalopram overdoses to other antidepressant overdoses do not demonstrate clinically meaningful differences in cardiotoxic effects"[10(p13)] and also that dose limitations in the FDA safety announcement "do not have strong clinical justification."[11(p13)]

Furthermore, in a cohort study of a US Department of Veterans Affairs database involving citalopram (N = 618,450) and sertraline (N = 365,898), Zivin et al[12] concluded that risks of ventricular arrhythmia, all-cause mortality, and noncardiac mortality were actually *lower* at citalopram doses > 40 mg/d than at daily doses of < 20 mg/d. Although not stated in the article, perhaps the implication is that undertreating depression carries a substantial risk of lethality.

The counterpunch came from a commentary by the FDA[13] that concluded "clinical trial data, case reports, and studies in animals provide clear evidence for dose-dependent QT prolongation with citalopram," and that the 18.5-millisecond prolongation at 60 mg/d remains of concern, "especially since this dosage was not more effective than 40 mg/day in clinical trials."(p18) (Most clinicians are aware that lack of statistical significance in clinical trials does not exclude the possibility that certain individuals may respond to higher doses.) The commentary by Zivin et al[14] followed immediately, noting that their study of over 600,000 patients taking citalopram found no increased risk of arrhythmias or mortality from any cause at doses > 40 mg/d compared to lower doses or to sertraline.

Ray et al[15] in the current issue of *JCP*, conducted a retrospective study of 54,220 Tennessee Medicaid outpatients treated with high doses of citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. The primary end point was sudden unexpected deaths, which included sudden cardiac deaths (n = 95), other cardiovascular deaths (n = 24), and unintentional drug overdose deaths (n = 26). The authors concluded that the risk of sudden unexpected death was not significantly greater for citalopram than for the other SSRIs. The fact that there were only 145 sudden unexpected deaths

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in such a large sample is testament to the overall safety of SSRIs. On the other hand, the number of sudden unexpected deaths associated with each of the 5 SSRIs was quite low, raising the possibility that the statistical lack of difference could represent a type II error, a false-negative finding.

As we await the next chapter in this ongoing controversy, remember that to override the FDA's edicts is to do so at your risk. There are always malpractice attorneys salivating in the background and ready to pounce. Nonetheless, there will be some clinical situations that clearly justify the use of higher than recommended doses. Due to variations in metabolism, blood levels of antidepressants can vary considerably among individuals taking identical doses. In addition, pharmacodynamic differences can be substantial. While the FDA commented that doses of citalopram over 40 mg/d "confer no additional benefit,"[3] clinicians are well aware that some patients tolerate and benefit from higher than recommended doses. Should one choose to increase citalopram above the 40-mg limit, he or she should do so only after discussing pros and cons with the patient, obtaining informed consent, and including documentation in the patient's chart. In addition, clinicians should be aware of the factors that may place patients at greater risk for malignant arrhythmias induced by antidepressants.

Finally, there are a considerable number of newer antidepressants (beyond tricyclics and monoamine oxidase inhibitors) on the market in addition to the SSRIs. Mago et al[16] have provided a qualitative review of the cardiovascular adverse effects of these medications (including SSRIs) that is highly recommended.

"One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."

Francis Weld Peabody[17(p367)]
(1881–1927)

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