Annals of Pharmacotherapy
47(10) 1330–1341

DOI: 10.1177/1060028013501994
aop.sagepub.com
SAGE

A Comparison of the Risk of QT Prolongation Among SSRIs

Kylee A. Funk, PharmD[1,2] and Jolene R. Bostwick, PharmD[1,2]

Abstract

Objective: To report QT prolongation potential in selective serotonin reuptake inhibitors (SSRIs) in order to advise clinicians on safe use of SSRIs other than citalopram in light of citalopram warnings. **Data Sources**: Primary literature and case reports were identified through a systematic search. Data from drug manufacturers, package inserts, and the ArizonaCERT database were also utilized. **Study Selection and Data Extraction**: English-language studies and case reports were included. **Data Synthesis**: Studies demonstrate possible dose-related clinically significant QT prolongation with escitalopram. Fluoxetine, fluvoxamine, and sertraline at traditional doses demonstrate a lack of clinically significant increases in QTc in the majority of studies. Further, paroxetine monotherapy shows a lack of clinically significant QTc prolongation in all studies. However, case reports or reporting tools still link these SSRIs with QTc prolongation. Fluoxetine, escitalopram, and sertraline used in post–acute coronary syndrome patients did not demonstrate risk of QTc prolongation. **Conclusion**: For clinicians who choose not to use citalopram due to recent Food and Drug Administration (FDA) recommendations, other antidepressants within this class may be considered. When citalopram is not utilized based on risk factors for TdP, use of escitalopram is not likely the safest alternative. Based on current literature, fluoxetine, fluvoxamine, and sertraline appear to have similar, low risk for QT prolongation, and paroxetine appears to have the lowest risk. However, there are significant limitations in interpreting the studies, including varying definitions of significant QT prolongation. Therefore, choice of an alternative SSRI should be based on individual risk factors for arrhythmias and other patient-specific factors.

Keywords
QTc prolongation, SSRI, torsades de pointes

Received 18 July 2013

Background

Since the late 1990s, more drugs have been removed from the market for concern over sudden cardiac death and ventricular arrhythmia than for any other adverse effect.[1] It is clear that arrhythmogenicity of medications should be examined as a potential safety concern. Studies have examined rates of sudden death among various antidepressants with varying conclusions.[1-3] Another method to study sudden death is examining risk of torsades de pointes (TdP), a potentially fatal arrhythmia.[4] Perhaps best summarized by Glassman and Bigger, "the QT interval is at best only modestly associated with torsade de pointes, but despite its difficulties it is the best predictor available."[4 (p.1775)]

The Food and Drug Administration (FDA) provides definitions of clinically relevant changes in QTc intervals.[5] Their guidance notes that a mean QTc increase of less than 5 ms does not appear to be associated with TdP; mean QTc increases from 5 to 20 ms have unclear associations with TdP, and medications that prolong the mean QTc interval by more than 20 ms show an increased risk for TdP. This same document indicates that clinically relevant individual changes from baseline in QTc may be defined as those greater than 30 or 60 ms.[5]

The arrhythmogenicity of certain selective serotonin reuptake inhibitors (SSRIs) have recently come under greater scrutiny.[6,7] In 2011, the FDA alerted the public and health care professionals to QT prolongation with citalopram use.[6] See Table 1 for details on new dosing limit recommendations.[6-8] This alert and associated recommendations on citalopram dosing raises questions regarding QT prolongation risk among various SSRIs. However, there are no current reviews or guidelines that address QT prolongation

[1]University of Michigan Health System, Ann Arbor, MI, USA
[2]University of Michigan College of Pharmacy, Ann Arbor, MI, USA

Corresponding Author:
Kylee A. Funk, Department of Pharmacy Services, University of Michigan Health System, University of Michigan College of Pharmacy, Victor Vaughn House, Room 324, 1111 E Catherine St, SPC 2054, Ann Arbor, MI 48109, USA.
Email: kafunk@med.umich.edu

Table 1. Summary of Recommendations From the FDA and MHRA.[6,7]

	FDA	MHRA
Do not use citalopram if the following apply	• Concomitant QT interval–prolonging medications • Congenital long-QT syndrome • Persistent QTc >500 ms • Bradycardia • Hypokalemia • Hypomagnesemia • Recent acute myocardial infarction Uncompensated heart failure	• Concomitant QT interval–prolonging medications • Congenital long-QT syndrome • QTc >500 ms Preexisting QT interval prolongation
Maximum dose of citalopram 20 mg	• Patients > 60 years old • Hepatic impairment • Poor CYP2C19 metabolizers Use of concomitant CYP2C19 inhibitors[a]	• Patients > 65 years old Hepatic impairment
Maximum dose of citalopram 40 mg	Adult patients	Adult patients
Do not use escitalopram if the following apply	No revised recommendations on dosing	• Concomitant QT interval–prolonging medications • Congenital long-QT syndrome • Preexisting QT interval prolongation QTc >500 ms
Maximum dose of escitalopram 10 mg	No revised recommendations on dosing	• Patients > 65 years old Hepatic impairment

Abbreviation: FDA, Food and Drug Administration; MHRA, British Medicines and Healthcare Products Regulatory Agency.
[a]Examples of CYP2C19 inhibitors: esomeprazole, fluconazole, fluoxetine fluvoxamine, ticlopidine, omeprazole, and voriconazole.[8]

among SSRIs other than citalopram. Although the FDA alert remains controversial, this review does not assess appropriate use of citalopram in light of the recent alert or the data surrounding QT prolongation with citalopram specifically.[9,10] Rather, it focuses on the risk of QT prolongation among other SSRIs to aid the clinician in safe selection of an alternative SSRI when, based on the new alert or other factors, the patient may not be a candidate for citalopram.

Data Sources

An English-language literature search was conducted of all articles in PubMed through June 2013. Search terms included individual SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) in combination with each of the following terms: *QTc, QT prolongation*, and *TdP*. Case reports and studies were selected whenever QT values were reported. Traditional dosing of SSRIs was primarily considered, and reports of QT prolongation with overdose were also examined. Nonhuman studies were excluded. In addition to the literature search, a request for information regarding QT prolongation was made to each of the companies that manufacture the individual SSRIs previously mentioned. Data from package inserts and from the database ArizonaCERT, a research group that publishes lists of QT-prolonging medications, were also included.

Results

Escitalopram

Escitalopram has been studied in several trials among various patient populations, including 1 study in post-myocardial infarction (MI) patients. Conflicting information from various agencies as well as information from medication resources are highlighted below.

Escitalopram is the *S*-enantiomer of racemic citalopram.[11] Whereas the FDA alert regarding citalopram specifies that the risk of QT prolongation does not apply to escitalopram, the British Medicines and Healthcare Products Regulatory Agency (MHRA) issued guidelines regarding both agents in December 2011.[6,7] See Table 1 for a summary of dose restriction recommendations from both the FDA and MHRA.

There are several studies that investigate QT prolongation associated with escitalopram. A retrospective review was recently published in *BMJ*, which used linear regression to examine any associations between antidepressants and QTc prolongation of more than 38 000 patients.[12] All SSRIs except fluvoxamine, certain tricyclic antidepressants (TCAs), certain serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and methadone (as a control) were examined. Escitalopram, citalopram, and amitriptyline showed a statistically significant dose-response correlation with QTc prolongation. An increase in escitalopram dose from 5 to 10 mg and from 10 to 20 mg showed an increased QTc interval of 11.0 ($P < .05$) and 4.7 ms ($P < .01$), respectively. In comparison, an increase in citalopram dose from 10 to 20 mg and from 40 to 60 mg showed an increase in QTc interval of 9.8 ($P < .001$) and 6.1 ms ($P < .01$), respectively, whereas an increase in amitriptyline from 25 to 50 mg showed an increase of only 3.4 ms ($P < .05$). The authors noted that the proportion of patients with QTc prolongation was similar among many of the antidepressants studied, and of those antidepressants that showed statistically significant QTc prolongation, the extent of the increase was small.[12]

The DECARD study was a prospective trial that examined the cardiovascular effects of prophylactic escitalopram in nondepressed patients after acute coronary syndrome

(ACS).[13] A total of 240 patients were randomized to receive placebo or escitalopram, 10 mg daily, and data were analyzed using intention-to-treat analysis. QT intervals were measured at baseline (399 and 398 ms), 6 months (395 and 391ms), and 1 year (396 and 388 ms) for patients receiving escitalopram and placebo, respectively. In both groups, a drop in the average QTc was seen from baseline measurement to 1 year, and no significant difference in QTc was found between the 2 groups.[13]

The package insert cites a study of 625 patients treated with escitalopram and 527 with placebo.[11] No patient in the escitalopram group had a QTc interval greater than 500 ms or a prolongation greater than 60 ms. However, there were no details regarding medication dosage, baseline QTc intervals, or background of the patients, which makes it difficult to interpret this study.[11]

Other doses of escitalopram were examined in a pharmacokinetic study referenced in the FDA citalopram alert and also in the drug package insert.[6,11] The study evaluates QTc intervals in healthy volunteers (n = 113) taking each of the following 3 regimens in a crossover design: (1) escitalopram in escalating doses from 10 to 30 mg daily, (2) moxifloxacin 400 mg daily, and (3) placebo daily. Baseline QTc was not reported, but changes in QTc were reported, and when the QT was corrected with Fridericia's formula, the 10–mg dose produced a prolongation of 4.5 ms, whereas the 30-mg dose produced a prolongation of and 10.7 ms.[6,11] Although the maximum recommended dose of escitalopram is 20 mg, it is noted that patients who are poor metabolizers of CYP2C19 and who take this dose could be exposed to steady-state concentrations similar to those found in healthy volunteers taking a 30-mg dose.[11]

In summary, certain large studies of patients taking escitalopram identify QTc prolongation, which appears to be dose related and most often is likely clinically insignificant. Additionally, 1 study conducted in post-MI patients failed to demonstrate QTc prolongation with escitalopram; however, the study used an intermediate dose.[13] On the other hand, a large retrospective study demonstrated average QTc prolongations greater than 5 ms, the package insert notes reports of TdP, and a case report demonstrated QTc prolongation with escitalopram in the absence of other QT-prolonging medications (further details are provided in Table 2).[11,12,14] Furthermore, whereas the FDA warnings state that there are no dose restrictions for escitalopram related to QT prolongation, the MHRA, ArizonaCERT, and the product package insert cite a risk of QT prolongation with escitalopram (Tables 1 and 2). [6,7,11,15] It appears that clinically significant QTc prolongation is rare but does occur, and escitalopram may be more likely to cause significant QTc prolongation when compared with fluoxetine, fluvoxamine, paroxetine, or sertraline.

Fluoxetine

Studies of fluoxetine that examine QT prolongation include 1 randomized, placebo-controlled trial in post–MI patients, several studies in depressed patients, and many small pharmacokinetic trials in healthy patients. Strik and colleagues[16] conducted a trial of 54 depressed patients 3 to 12 months post-MI who were randomized to receive fluoxetine 20 mg daily (with the option to increase to 60 mg daily) or placebo. Baseline mean QTc measurements were reported for the fluoxetine group (417 ms) and placebo group (414 ms). The authors did not report other QTc measurements but did note that the 27 patients randomized to fluoxetine treatment (mean dose of 47.3 mg daily) had no change in the QTc interval from baseline during the initial 9-week time frame when electrocardiogram (ECG) data were analyzed.[16]

Studies that review fluoxetine's effects on the QT interval in depressed patients were found to have low enrollments. Upward and colleagues[17] compared the cardiac effects of fluoxetine 40 mg daily increased to 60 mg daily after 1 week (with the option to titrate to 80 mg daily at week 2) and amitriptyline in 23 depressed patients. In the 11 patients randomized to fluoxetine, the QTc interval showed a nonsignificant trend toward increasing, from a QTc of 401 (±5) ms at baseline to 411(±4) ms after 4 weeks of treatment.[17] In a similar study, Baker et al[18] examined the cardiac effects of fluoxetine and doxepin in patients with major depressive disorder (MDD). In all, 20 patients were started on fluoxetine 20 mg daily and titrated to a maximum dose of 60 mg daily (average daily dose was 36.8 mg). The QTc increased from 428 ms at baseline to 430 ms after 6 weeks, and the authors concluded that the change represents no effect.[18] Another trial of the cardiac effects of fluoxetine in depressed patients was conducted by Roose et al,[19] but this trial differs from the previous two examined, in that patients had concomitant heart disease. Varying doses (up to 60 mg) of fluoxetine were studied in 27 patients. QTc was assessed in a subset of patients who had a baseline QRS interval ≥0.10 s (n = 18). Results demonstrated that there was a nonsignificant increase in the QTc interval from 441(±39) ms to 450(±32) ms ($P = .17$) from baseline to 2 weeks of treatment;

although the QTc interval was not reported at the end of the study (week 7), the authors noted that there was no significant increase.[19]

Several small pharmacokinetic studies conducted in healthy patients further validate the findings from the trials of fluoxetine in patients with depression or cardiac abnormalities. In a study by Zhao et al,[20] 12 volunteers were given cisapride 10 mg 4 times daily for 6 days with a washout period of 7 days, followed by fluoxetine 20 mg daily for 31 days, followed by 7 days of concomitant cisapride and fluoxetine at the doses previously given. Of note, the only statistically significant change in QTc from baseline

Table 2. Case Reports of QTc Prolongation Linked to SSRIs.

SSRI	Patient	TdP Risk Factors Reported	Non–QT-Prolonging Medications	Concomitant QT-Prolonging Medication[a]	Details (QTc in ms)
Escitalopram	42-Year-old woman with a manic episode	No heart disease, electrolytes within normal limits	Lorazepam and clonazepam; valproate stopped and held prior to QTc of 446 ms	Quetiapine stopped and held prior to QTc of 446 ms	QTc was 446 ms prior to escitalopram 5 mg and 503 ms 2 days after, at which point escitalopram was stopped. 3 Days after stopping, the QTc was 441 ms[14]
Fluoxetine	59-Year-old woman	No cardiac history (except hypertension), electrolytes within normal limits prior to surgery. After cardioversion and surgery, potassium = 3.3 mEq/L and magnesium= 5.6 mg/dL (patient received magnesium while in TdP)	Prior to surgery: cyclobenzaprine (substrate of CYP3A4 and CYP2D6), amlodipine, diclofenac, and triamterene; in preparation for surgery, the patient received metoclopramide, cefazolin, atracurium, bupivacaine, fentanyl, flurane, ketorolac, lidocaine, metoclopramide, midazolam, nitrous oxide, and propofol	Droperidol in preparation for surgery	QTc with fluoxetine 30–mg daily and cyclobenzaprine was 497 ms. Patient developed TdP during surgery (QTc was 500 ms postcardioversion). On postoperation day 1, cyclobenzaprine was discontinued, and QTc decreased to 440 ms. The authors noted that fluoxetine's inhibitory effects of CYP3A4 and CYP2D6 may have increased cyclobenzaprine concentration and suggest that high serum levels of cyclobenzaprine may be associated with arrhythmias[23]
	49-Year-old woman	Potassium = 2.8 mEq/L on starting antibiotic therapy but corrected to 3.5 and 3.4 mEq/L on subsequent days; potassium within normal limits when QTc was prolonged	Hydrochlorothiazide, gabapentin, propranolol, and carisoprodol. Then, a course of ceftriaxone was added as well as loratadine and ferrous sulfate	Prior to antibiotics, imipramine (CYP2D6 substrate) and mirtazapine; then, a course of levofloxacin and pseudoephedrine	Patient taking fluoxetine 10 mg daily; QTc was 509 ms after 5 days of antibiotic therapy. Once levofloxacin was discontinued, QTc was 403 ms. Through CYP2D6 inhibitory effects, fluoxetine may have increased imipramine concentration[24]
	41-Year-old woman	No cardiac history reported, potassium=4.5 mEq/L, magnesium= 1.5 mg/dL	Alendronate, vitamin D, and calcium supplements	Levomethadyl (CYP 3A4 substrate); the patient was also noted to be abusing IV cocaine and cannabinoids	Patient taking fluoxetine 20 mg daily; she developed TdP, and after postcardiac conversion, was found to have a QTc of 710 ms. The authors note fluoxetine inhibits CYP3A4 and may have resulted in increased serum levels of levomethadyl[25]
	Infant born to fluoxetine-treated mother	Infant's electrolytes within normal limits; only cardiac abnormality was a mild systolic murmur	Mother also taking levothyroxine	None	Mother was taking 30 mg fluoxetine daily. Infant's QTc was 540-580 ms at 30 hours. Days after birth, QTc was 380-360 ms and at 2 months, QTc was 420 ms[26]

(continued)

Table 2. (continued)

SSRI	Patient	TdP Risk Factors Reported	Non–QT-Prolonging Medications	Concomitant QT-Prolonging Medication[a]	Details (QTc in ms)
	52-Year-old man	Electrolytes within normal limits	Verapamil	None	QTc was 380 ms prior to fluoxetine. After fluoxetine 20 mg daily for 2 weeks followed by 40 mg daily for 2.5 months, QTc was 560 ms, and fluoxetine was discontinued. QTc 10 days after discontinuation of fluoxetine was 380 ms[27]
	83-Year-old woman	Electrolytes within normal limits; patient found to have left bundle branch block	Aspirin	None	After taking fluoxetine 20 mg daily for 6 months, patient with left bundle branch block and QTc of 478 ms experienced recurrent short episodes of TdP. Fluoxetine was discontinued. Two months after discontinuation, QTc was 421 ms; 8 months after discontinuation, QTc was 408 ms[28]
Fluvoxamine	13-Year-old girl	No cardiac abnormalities; potassium level within normal limits; magnesium noted to be 1.5 mg/dL	None	None	After taking fluvoxamine 75 mg daily for 4 months, QTc was found to be between 460 and 490 ms. Once the dose was decreased to 50 mg, the QTc was no longer prolonged[36]
Paroxetine					No reports found in systematic search
Sertraline	26-Year-old man	No cardiac history reported	Atenolol and lorazepam	Clozapine, risperidone, pseudoephedrine	Patient taking sertraline 200 mg daily; found dead with therapeutic concentrations of medication in his body. Most likely cause of death was sudden death caused by arrhythmia. EKG 5 years prior to his death showed a QTc of 437 ms. Authors note that sertraline is an inhibitor of 4 CYP enzymes that metabolize clozapine.[51] In addition, sertraline may inhibit risperidone's metabolism
	72-Year-old woman	Electrolytes within normal limits	Digoxin and acenocumarine (also known as acenocoumarol)	Sotalol	Patient taking unknown dose of sertraline; presented to hospital and was found to have prolonged QT interval and developed TdP[52]
	49-Year-old man	Potassium =3.1 mmol/L	Hydrochlorothiazide, NPH insulin, regular insulin, naproxen, and oxycodone	Doxepin and vorinostat	After hematochezia, hematemesis, and syncopal episode, patient presented to hospital. QTc was 826 ms (48 months prior to admission, QTc was 400 ms). Patient developed TdP[53]

Abbreviations: SSRI, selective serotonin reuptake inhibitors; TdP, torsades de pointes; NPH, neutral protamine Hagedorn.
[a]Considered a QT-prolonging medication if it is on the ArizonaCERT list.

occurred when patients received cisapride alone; there were no significant differences in QTc during the other phases. When the patients received 31 days of treatment with 20 mg of fluoxetine daily, the average QTc showed a nonsignificant increase from 416 ms at baseline to 419 ms, and 406 ms at baseline to 407 ms when corrected by Bazett's and Sagie's formula, respectively. It is notable that 3 patients had a QTc increase greater than 15% from baseline, and 2 of these instances occurred when patients were in the fluoxetine monotherapy treatment phase.[20] Another small study evaluated the pharmacokinetic parameters of 3 regimens in healthy participants: (1) racemic fluoxetine, (2) 80 mg daily of the *R*-enantiomer of fluoxetine, (3) 80 mg daily for 1 week followed by 120 mg daily for 4 weeks of the *R*-enantiomer of fluoxetine.[21] Four individuals received racemic fluoxetine 60 mg daily for 1 week followed by 20 mg daily for 4 weeks, and the average QTc decreased from 418 ms at baseline to 417 ms at week 5. Of note, those taking 120 mg of the *R*-enantiomer of fluoxetine (n = 4) experienced an increase in QTc from an average baseline of 413 to 457 ms at week 5, whereas individuals taking 80 mg of the *R*-enantiomer had a much smaller increase in QTc (from a baseline of 421 to 427 ms at week 5).[21] Although the *R*-enantiomer is not currently marketed and patients would not be exposed to the high levels of the *R*-enantiomer with traditional fluoxetine dosing, the results do indicate that QTc effects are likely dose related and also may differ among enantiomers.

In summary, no QTc prolongation was seen in the trial of post-MI patients treated with fluoxetine.[16] In the other studies, median QTc changes from baseline ranged from slight decreases to non–statistically significant increases up to 10 ms at therapeutic doses of 20 to 80 mg daily. Despite few reports of QTc prolongation in these studies, the package insert does cite postmarketing cases of TdP, and there are several case reports of QTc prolongation with fluoxetine used both with and without other QT-prolonging medications (Table 2).[22-28] The number of case reports should not necessarily be reviewed as a reflection of fluoxetine's risk relative to other SSRIs because of its extended time on the market. Additionally, both the ArizonaCERT database and package insert identify a risk of QT prolongation with fluoxetine.[15,22] Current studies do not show statistically significant increase in QTc interval, but case reports demonstrate a rare risk of QTc prolongation caused by fluoxetine.

Fluvoxamine

Fluvoxamine's effect on the QT interval has been examined in 2 large, linear regression studies and also in studies that compare its risk to TCAs.

Regression analysis of fluvoxamine's association with QT prolongation was analyzed in 2 separate studies of Japanese patients. Okayasu et al[29] conducted a study evaluating 729 patients. A total of 70 study patients were taking fluvoxamine as an antidepressant at a mean dose of 105.4 mg daily. After the authors controlled for age, sex, and other psychotropic medications, use of fluvoxamine was not found to be a significant risk factor for QTc prolongation (regression coefficient = −6.55; 95% CI = 15.01-1.90; $P \geq .05$).[29] Another similar study looked at the QT interval in 688 Japanese patients with psychiatric conditions.[30] Of these patients, 34 were treated with fluvoxamine at an unreported dose—either as monotherapy (n = 23) or in combination with another psychotropic medication (n = 11). Through regression analysis, it was found that fluvoxamine was not a significant risk factor for QTc prolongation (adjusted odds ratio = 1.47; 95% CI = 0.92-2.35; $P = .11$).[30]

Several studies compare TCAs with fluvoxamine. One study by Hochberg et al[31] compared cardiovascular effects of TCAs (n = 100) with fluvoxamine (n = 311) in depressed patients.[31] Although the mean QTc values were not reported, changes in QTc from baseline after 1 year of treatment with fluvoxamine versus TCA were found to be 1 (±36) ms and 21 (±50) ms, respectively. Whereas the change in QTc for fluvoxamine was not significant, it was significant for TCAs ($P = .002$).[31] Rodriguez de la Torre et al[32] also examined cardiovascular effects of TCAs and SSRIs in inpatients treated for depression. Baseline QTc intervals were not presented, but it was noted that patients with ECG abnormalities prior to treatment with a study drug were excluded. In all, 14 patients were treated with fluvoxamine at an average dose of 89 mg daily. QTc measurements were taken after patients were at steady state, which the authors report as following 14 days of treatment generally. QTc prolongation, defined as a QTc greater than 440 ms, was noted in 4 fluvoxamine-treated patients; however, the extent of QTc prolongation was not reported.[32] Furthermore, Laird et al[33] compared imipramine's (n = 14) cardiovascular effects with that of fluvoxamine (n = 17) and placebo (n = 15) in patients with depression. QTc for fluvoxamine was unchanged during the study; the QTc interval was 410 ms at both baseline and week 6, whereas the average QTc for imipramine showed a statistically significant increase of 20 ms during this time period.[33] Finally, a similar study compared the cardiovascular effects of maprotiline (n = 15) with that of fluvoxamine 200 mg daily (n = 18) in patients with MDD.[33] The QTc interval average was 378 ms prior to fluvoxamine treatment and 380 ms after 21 days of treatment (*P* value was reported as not significant).[34]

In summary, regression studies for fluvoxamine fail to associate the drug with QTc prolongation.[29,30] One study reported QTc levels greater than 440 ms in 4 of 14 patients; however, the significance of this finding is unclear because baseline QTc values were not reported.[32] In the other studies, QTc prolongation was either nonexistent or only averaged 1 to 2 ms. The ArizonaCERT database does not include fluvoxamine on any of its lists of QT-prolonging drugs, but

the package insert indicates risk in association with other QT-prolonging medications as well as postmarketing reports of TdP.[15,35] Despite negligible risk in studies and databases, there is 1 case study that reports QTc prolongation with fluvoxamine in monotherapy (Table 2).[36] Studies do not demonstrate clinically significant QTc prolongation; however, there appears to be a rare risk of QTc prolongation and TdP from case and postmarketing reports.

Paroxetine

Studies of paroxetine in which the QT interval was examined include a linear regression analysis, those in patients with depression or panic disorder, and studies of drug interactions that may increase the risk of QT prolongation.

Through the same linear regression model previously referenced, Okayasu et al[29] analyzed paroxetine's effect on QTc prolongation. The authors examined QTc intervals for inpatients taking antidepressants. Paroxetine (n = 129) was used at an average daily dose of 22.5 mg and was not found to be a significant risk factor for QTc prolongation (regression coefficient = 1.05; 95 % CI = −6.97 to 9.07; $P \geq .05$).[29]

The QTc interval of paroxetine was compared with that of placebo, a TCA, or an SNRI in several studies in patients with depression. Paroxetine was compared with duloxetine in a pooled analysis of four 8-week trials.[37] Patients with MDD were randomly assigned to placebo (n = 371), paroxetine 20 mg daily (n = 359), or duloxetine (n = 736). Patients in the paroxetine group had a baseline QTc of 405.7 ms and a QTc of 404.7 ms at the end of the study. The authors found no significant change in the QTc in any of the groups.[37] Kuhs and Rudolf[38] conducted a randomized trial of paroxetine 30 mg daily (n = 20) versus amitriptyline 150 mg daily (n = 20) in patients with MDD over 6 weeks. Amitriptyline significantly prolonged the QTc interval from baseline, but paroxetine's effects on the QTc interval were not significant at 3 weeks (QTc = 410 ms) or 6 weeks (QTc = 414 ms) compared with baseline (QTc = 418 ms).[38] Furthermore, the effect of paroxetine 30 mg daily on the ECG was analyzed in a placebo-controlled study of patients with major depression (n = 20).[39] For those treated with paroxetine, baseline QTc was 407 ms, and QTc after 4 weeks of treatment was 404 ms; this decrease was not significant.[39] Rodriguez de la Torre et al[32] not only studied fluvoxamine as previously referenced but also studied paroxetine in inpatients treated for depression. Baseline QTc intervals were not presented, but it was noted that patients with ECG abnormalities prior to treatment with a study drug were excluded. Of the 19 patients treated with paroxetine—at an average dose of 33 mg daily—there were no ECG abnormalities after about 14 days of treatment.[32]

Paroxetine's effects on the QT interval were also evaluated in patients with panic disorder. Yerangi et al[40] assessed the effects of both nortriptyline (n = 13) and paroxetine (n = 16) on QT intervals.[40] Over the 15 (±5.3) week trial, patients received an average daily dose of 19.7 mg of paroxetine. Patients taking paroxetine had a decrease in their QT interval mean from a baseline of 426 to 410 ms, which was not significant.[40]

Several pharmacokinetic studies of paroxetine were also examined. Because paroxetine is a weak CYP3A4 inhibitor, its effect on terfenadine—a CYP3A4 substrate (which has been withdrawn from the U.S. market) known to prolong the QT interval—was studied in an open-label crossover trial (n = 12).[41] Not only did the addition of paroxetine 20 mg daily to terfenadine have no effect on the QTc interval, but its effect on inhibition of terfenadine's metabolism did not influence the QTc interval.[41] Paroxetine is also considered a strong CYP2D6 inhibitor, and its interaction with iloperidone, a CYP2D6 substrate, was studied in 183 patients with schizophrenia or schizoaffective disorder.[42] When 20 mg of paroxetine was added to varying doses of iloperidone, QTc prolongation ranged from an average of 11.2 ms at a dose of iloperidone 8 mg, twice daily, up to 17.5 ms for an iloperidone dose of 24 mg daily. When paroxetine monotherapy was added to iloperidone, two patients experienced a QTc prolongation greater than 60 ms, and no patient had a QTc interval greater than 500 ms. It should be noted that QT prolongation has been associated with iloperidone, and in this study, QT intervals increased with greater iloperidone concentrations.[42] In a similar study, paroxetine's interaction with flecainide—a CYP2D6 substrate and antiarrhythmic agent, which prolongs the QT interval—was studied in 21 healthy volunteers with CYP2D6 genotypes, which ranged from poor to extensive metabolizers.[15,43] When paroxetine was added to flecainide, there was a statistically significant increase in QTc in each of the metabolizer subtypes.[43] It is unclear from this study if paroxetine alone had effects on the QTc or if the majority of effects were the result of increased serum concentrations of flecainide from the CYP2D6 interaction with paroxetine.

In summary, the only instance of QTc prolongation with paroxetine was found in combination with other QT-prolonging medications. In addition, no case studies of paroxetine in monotherapy or with other QT-prolonging medications were found in a systematic search. The ArizonaCERT lists paroxetine as a risk of QT prolongation in certain situations, and the package insert notes risk when used with other medications, including thioridazine and pimozide.[15,44] Based on these data, it can be concluded that paroxetine does not cause clinically significant QTc prolongation when used without interacting medications.

Sertraline

Sertraline's effects on the QT interval have been studied in a variety of populations, including healthy individuals and patients with obsessive compulsive disorder (OCD), mood

disorders, depression with psychotic features, or depression post-acute MI or unstable angina.

One of the larger reports of sertraline's effects on the QT interval was published by Guy and Silke,[45] who conducted a review of 4 studies that compared sertraline with amitriptyline and/or placebo. A total of 2500 ECGs were analyzed; 456 of the ECGs were for patients treated with sertraline. QTc values were not reported, but it was reported that sertraline did not affect the QTc interval. The authors also examined the QTc intervals for the subset of patients older than 65 years of age and found that although amitriptyline caused a statistically significant increase, sertraline showed no effect.[45]

Another large study that looked at the effects of sertraline on the QT interval was the SADHART trial, a prospective trial of 369 patients with MDD, who had an acute MI or were hospitalized with unstable angina within 30 days of enrollment.[46] Patients were randomized to placebo (n = 183) or sertraline (n = 186) after their MI or unstable angina event. The average daily dose of sertraline was 68.8 mg (range = 50-200 mg). After 16 weeks of treatment, there was no statistically significant difference in the QTc from baseline, with QTc values of 418 and 420 ms, respectively. Additionally, the number of patients with a QTc greater than 450 ms in both the treatment and control groups decreased during this period.[46]

Sertraline was also studied in patients with OCD. Wilens et al[47] reported on a multicenter study evaluating sertraline versus placebo in 187 adolescents and youths with OCD. Participants were randomized to placebo (n = 95) or sertraline (n = 92) 25 to 200 mg daily. The average daily dose of sertraline was 167 mg. QTc values were not reported, but it was reported that no difference in QTc was seen between baseline and 16 weeks. The authors note that 2 patients developed QTc ≥ 440 ms, but no patient's QTc increased beyond 460 ms.[47]

Sertraline's association with QT prolongation was also studied in the regression analysis in patients with mood disorders previously cited by Okayasu et al.[29] The authors concluded that sertraline (n = 20) at an average daily dose of 53.8 mg was not a risk factor for QTc prolongation (regression coefficient = −0.34; 95 % CI = −20.64 to 19.96; $P \geq .05$).[29]

A dose-finding study of sertraline looked at 30 patients with major affective disorder randomized to placebo or sertraline 50, 100, or 200 mg.[48] There were no clinically significant ECG changes in the placebo or 50-mg sertraline groups. In the 100–mg sertraline group, there was 1 patient with a ventricular arrhythmia, and in the 200-mg sertraline group, 1 patient had a clinically significant increase in QTc. However, the authors did not define a clinically significant change in QTc, and QTc values were not reported.[48]

In addition to the effects sertraline monotherapy has on the QT interval, drug interactions involving sertraline that may lead to QT prolongation have also been examined. In 1 study, patients with major depression with psychotic features (n = 17) were treated with both ziprasidone, a known QT-prolonging medication, and sertraline at average daily doses of 81.5 and 167.9 mg, respectively.[49] The average QTc increased from 410 ms at baseline to 424.9 ms after 29 days of combination treatment ($P = .04$).[49] Alderman[50] looked at the interactions between 200 mg sertraline daily and cisapride or pimozide, which are both known to increase the QT interval. Because sertraline is a CYP3A4 inhibitor, it may increase the concentration of cisapride or pimozide (both CYP3A4 substrates), which might, in turn, lead to an increased risk for QT prolongation. After coadministration of sertraline, in both the pimozide and cisapride groups, there was no patient with a QTc increase greater than 15% from baseline to the end of the study. One patient in the pimozide group had a QTc interval greater than 450 ms (the interval was 453 ms, which was an increase from 421 ms at baseline).[50]

In summary, studies show potentially clinically significant QT prolongation only when sertraline is taken concomitantly with other QT-prolonging medications. Results of published case reports agree with these studies, in that QTc prolongation is only reported for sertraline in the presence of other QT-prolonging medications (Table 2).[51-53] However, the ArizonaCERT notes risk of QT prolongation under certain conditions, and the package insert mentions postmarketing reports of QT prolongation and TdP, but sertraline's direct association with these postmarketing reports is unclear.[15,54] Based on postmarketing data, sertraline may have a rare risk of QTc prolongation.

Discussion

On review of the various trials that examine QT prolongation among SSRIs, it is apparent that many studies of SSRIs given within the labeled dosage range fail to demonstrate statistically and clinically significant increases in QTc. Nevertheless, it is now difficult to define what extent of QTc increase should be deemed clinically significant. The FDA previously suggested categories for clinically significant increases in mean QTc from baseline as those greater than 20 ms or for individual increases from baseline as those greater than 30 or 60 ms.[5] Despite this guidance, dosage restrictions for citalopram appear to be based on a referenced average QTc increase of 18.5 ms, a prolongation that is considered to have an unclear association with TdP.[5,6] Whereas most SSRIs reveal no increase in QTc or increases much less than 20 ms, it is difficult to categorize this prolongation in light of conflicting guidance from FDA publications and the existing alert.

In addition to the ambiguity of the definition of a clinically significant increase in QTc, it is challenging to fully assess the data presented in this review because of the

significant limitations of these trials. More specifically, many of these trials were not designed to examine QTc changes. This design is often associated with missing details such as baseline QTc, extent of prolongation, and measurements of statistical significance. Furthermore, risk factors for TdP such as age, female gender, presence of hypokalemia, hypomagnesemia, bradycardia, and cardiovascular disease were often also not reported.[55] In addition, many studies were small pharmacokinetic analyses, which may not be generalizable to a broad population; did not always use a broad range of doses, which might be seen in treatment of other diseases such as anxiety disorders; may not have been powered to show significant differences in QTc intervals; and almost certainly were not powered to predict risk of TdP. Furthermore, it is difficult to compare or pool data for more meaningful results because of variation of clinician QTc interpretations as well as the use of different correction factors, which lead to a difference in reported values.[55] Finally, although there are detailed guidelines on methodology for thorough QT/QTc studies, including recommendations for a prospective, placebo-controlled study, to our knowledge, no thorough QT/QTc studies of SSRIs have been published in peer-reviewed literature.[5] The availability of such studies could facilitate comparisons among agents to better assist clinicians in interpreting risk. Despite these limitations, this review informs clinicians about the use of SSRIs in certain at-risk populations.

Current literature indicates that risk for QT prolongation or TdP is reported more frequently with citalopram and escitalopram, whereas the risks associated with fluoxetine, fluvoxamine, paroxetine, and sertraline are largely limited to case reports. Based on the literature and case reports, paroxetine has the lowest risk for QT prolongation among the SSRIs. Because many studies already presented show a very low risk for QT prolongation and yet there is still reported risk for many SSRIs, we can surmise that the risk occurs in rare cases. Case reports that demonstrate QTc prolongation in SSRI use with and without concomitant QT-prolonging medications are outlined in Table 2. From the limited number of case reports available, it is difficult to draw conclusions other than to infer that there are likely rare risks of QT prolongation with escitalopram, fluoxetine, and fluvoxamine used in monotherapy (Table 2). Although it is difficult to deduce the influence of the particular SSRI in the case reports that include concomitant medications that may also prolong the QT interval, information provided may be useful when considering risk of QT prolongation in patients receiving multiple agents that may increase this risk.

Because the incidence of QT prolongation among these agents as well as the risk for TdP is rare and may be underreported in the literature, a review of the ArizonaCERT database reveals additional information. The database does not categorize fluvoxamine as having any QT risk, categorizes fluoxetine, paroxetine, and sertraline as having QT prolongation or TdP risk under certain conditions, and categorizes escitalopram as a drug that is generally accepted to have a risk of TdP.[15]

When overdose situations are examined, QT prolongation has been reported with each SSRI, with the exception of paroxetine.[22,35,44,54,56-58] The preponderance of QT prolongation in case reports of overdose with very few citations of QT prolongation with traditional dosing suggests a dose-related effect for QT prolongation caused by SSRIs. The dose-related QT prolongation is also supported by studies that show greater prolongation of the QTc interval in citalopram and escitalopram at larger doses.[6,12]

Certain populations at higher risk for complications from QT prolongation have been studied. For instance, QT prolongation was examined when post-ACS patients were given escitalopram, fluoxetine, or sertraline.[13,16,46] In the study of sertraline, patients had existing depression, whereas in the study of fluoxetine, patients developed depression after their ACS episode; finally, escitalopram was used prophylactically in nondepressed patients in the DECARD study. In each of these studies, no QTc prolongation was detected.[13,16,46] Based on these trials, all 3 of these SSRIs could likely be used safely in post-ACS patients.

Some interesting considerations in medication selection were identified in this review. One such consideration is the effects of enantiomers versus the racemate. Henry et al[21] compared the pharmacokinetics of the fluoxetine *R*-enantiomer versus the racemate and found differences in QTc effects between the 2 enantiomers. Likewise, the FDA presented 2 similar studies of QTc prolongation in citalopram and escitalopram in the recent citalopram alert.[6] Although escitalopram is the *S*-enantiomer of citalopram, the QT prolongation effects of escitalopram are not highlighted in the FDA warning, although other agencies do note a potential risk.[6,7] Another consideration of interest is the role of genetics in medication safety. In the FDA warning of citalopram, the FDA created dose restrictions for patients who are poor CYP2C19 metabolizers, and the package insert for escitalopram notes that patients who are poor CYP2C19 metabolizers may be exposed to supratherapeutic levels when they are taking the maximum recommended dose.[6,11] Use of genetic tests to identify metabolizer status is not currently a standard of practice. This lack of information may make clinicians uncertain about how to apply this information or may place certain patients who are poor metabolizers without access to genetic testing at greater risk for QT prolongation.

The lack of clear data regarding QT prolongation caused by SSRIs leaves the clinician with many questions when choosing an appropriate SSRI. Even the FDA warning for citalopram is controversial; both previous and current studies suggest that citalopram is likely not associated with TdP.[9,59,60] Furthermore, the FDA warning was based on a

small study that demonstrated QTc increases below the previously recognized threshold for concern.[5,6] Larger studies that are designed to assess QTc prolongation must be conducted to more clearly define the risk for all SSRIs. It is difficult to design a study large enough to assess for TdP; thus, the clinician must rely on data from case reports and data reported to manufacturers. It is important for clinicians to continue to report cases of QTc prolongation and TdP associated with SSRIs, so the medical community can gain a better understanding of the potential risks.

Citalopram was often regarded as a first-line SSRI because of its favorable side effect profile, low rate of drug interactions, and low cost. However, with the new restrictions on citalopram use, clinicians are faced with difficult decisions to potentially withhold a beneficial medication or perhaps face litigation.[9] Many clinicians may choose to consider what alternative SSRIs could be used, but based on the currently available data, there is no clear, preferred alternative. Because of the ambiguity of the data, we propose that alternatives to citalopram can be chosen based on risk versus benefit as well as the following factors:

- Because of its low cost, tolerability, and drug interaction profile, citalopram should still be considered and used within the scope of the new FDA recommendations, including appropriate ECG, electrolyte, and other laboratory monitoring, especially in patients at risk for QT prolongation.[6] The authors note the importance of assessing risk versus benefit of therapy in patients currently managed on higher doses of citalopram.
- If the patient has recently experienced ACS, fluoxetine, escitalopram, or sertraline should be considered first-line SSRIs because of their lack of documented effect on the QT interval in this population.[13,16,46]
- Apart from risks when using citalopram, there is no clear difference in QTc prolongation risk among other SSRIs based on currently available data. With that stated, use of escitalopram may be regarded with particular caution given the MHRA warning.[7,12] In the absence of other interacting medications, clinicians may consider using paroxetine in patients with risk factors for TdP. However, apart from TdP risk factors, selection of the optimal SSRI should be made with consideration of drug-related factors, including patient preference, tolerability, interactions, cost, and so on.[61]
- Elderly patients may be at particular risk for QT prolongation.[55] Because of the limited data, specific recommendations regarding SSRI selection and QT risk in this population cannot be made. However, clinicians may consider age-specific warnings from the FDA as well as MHRA guidelines, which recommend a maximum escitalopram dose of 10 mg in this population (refer to Table 1).[6,7] Caution and close monitoring are recommended.
- Non-SSRI first-line antidepressants such as SNRIs, mirtazapine, and bupropion should be reviewed for their risk of QT prolongation, and based on findings from these reviews, they could be alternatives for patients at risk for TdP.[62]

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiol Drug Saf*. 2011;20:903-913. doi:10.1002/pds.2181
2. Weeke P, Jensen A, Folke F, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. *Nature*. 2012;92:72-79. doi:10.1038/clpt.2011.368.
3. Martinez C, Assimes TL, Mines D, Dell'aniello S, Suissa S. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. *BMJ*. 2010;340:c249. doi:10.1136/bmj.c249.
4. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158:1774-1782.doi:10.1176/appi.ajp.158.11.1774
5. US Department of Health and Human Services. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. http://www.fda.gov/downloads/ RegulatoryInformation/Guidances/ucm129357.pdf. Accessed March 23, 2013.
6. US Food and Drug Administration. FDA drug safety communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm. Accessed November 18, 2012.
7. Medicines and Healthcare Products Regulatory Agency. Citalopram and escitalopram: QT interval prolongation: new maximum daily dose restrictions (including in elderly patients), contraindications and warnings. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137769. Accessed March 23, 2013.
8. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors, and inducers. http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Accessed May 12, 2013.

9. 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;125:859-868. doi:10.1016/j.amjmed.2011.12.002.
10. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 1. *J Psychosoc Nurs Ment Health Serv*. 2011;49:13-16. doi:10.3928/02793695-20111011-01.
11. Lexapro (escitalopram) [product information]. St Louis, MO: Forest Pharmaceuticals, Inc; 2012.
12. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288. doi:10.1136/bmj.f288.
13. Hanash JA, Hansen BH, Hansen JF, Nielsen OW, Rasmussen A, Birket-Smith M. Cardiovascular safety of 1-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome. *J Cardiovasc Pharmacol*. 2012;60:397-405.doi:10.1097/FJC.0b013e3182677041.
14. Tseng PT, Lee Y, Lin YE, Lin PY. Low-dose escitalopram for 2 days associated with corrected QT interval prolongation in a middle-aged woman: a case report and literature review. *Gen Hosp Psychiatry*. 2012;34:210.e13-210.e15. doi:10.1016/j.genhosppsych.2011.10.005.
15. Arizona CERT. QT drug lists by risk groups. http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm. Accessed March 23, 2013.
16. Strik JJMH, Honig A, Lousberg R, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a doubleblind, placebo-controlled trial. *Psychosom Med*. 2000;62:783-789.
17. Upward JW, Edwards JG, Goldie A, Waller DG. Comparative effects of fluoxetine and amitriptyline on cardiac function. *Br J Clin Pharmacol*. 1988;26:399-402.
18. Baker B, Dorian P, Sandor P, et al. Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. *J Clin Psychopharmacol*. 1997;17:15-21.
19. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT Jr. Cardiovascular effects of fluoxetine patients with heart disease. *Am J Psychiatry*. 1998;155:660-665.
20. Zhao Q, Wojcik MA, Parier JL, Pesco-Koplowitz L. Influence of coadministration of fluoxetine on cisapride pharmacokinetics and QTc intervals in healthy volunteers. *Pharmacotherapy*. 2001;21:149-157. doi:10.1592/phco.21.2.149.34109.
21. Henry ME, Schmidt ME, Hennen J, et al. A comparison of brain and serum pharmacokinetics of R-fluoxetine and racemic fluoxetine: a 19-F MRS study. *Neuropsychopharmacology*. 2005;30:1576-1583. doi:10. 1038/sj.npp.1300749.
22. Prozac (fluoxetine) [product information]. Indianapolis, IN: Eli Lilly and Company, Jan 2013.
23. Michalets EL, Smith LK, Van Tassel ED. Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother*. 1998;32:761-765. doi:10.1345/aph.17351.
24. Nykamp DL, Blackmon CL, Schmidt PE, Roberson AG. QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother*. 2005;39:543-546. doi:10.1345/aph.1E513.
25. Deamer RL, Wilson DR, Clark DS, Prichard JG. Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM). *J Addict Dis*. 2001;20:7-14. doi:10.1300/J069v20n04_02.
26. Dubnov G, Fogelman R, Merlob P. Prolonged QT interval in an infant of a fluoxetine treated mother. *Arch Dis Child*. 2005;90:972-973. doi:10.1136/adc.2004.064618.
27. Varriale P. Fluoxetine (prozac) as a cause of QT prolongation. *Arch Intern Med*. 2001;161:612.
28. Wilting I, Smals OM, Holwerda NJ, Meyboom RH, de Bruin ML, Egberts TC. QTc prolongation and torsades de pointes in an elderly woman taking fluoxetine. *Am J Psychiatry*. 2006;163:325. doi:10.1176/appi.ajp.163.2.325.
29. Okayasu H, Ozeki Y, Fujii K, et al. Pharmacotherapeutic determinants for QTc interval prolongation in Japanese patients with mood disorder. *Pharmacopsychiatry*. 2012;45:279-283. doi:10.1055/s-0032-1308969.
30. Sadanaga T, Sadanaga F, Yao H, Fujishima M. Abnormal QT prolongation and psychotropic drug therapy in psychiatric patients: significance of bradycardia-dependent QT prolongation. *J Electrocardiol*. 2004;37:267-273. doi:10.1016/j.jelectrocard.2004.07.001.
31. Hochberg HM, Kanter D, Houser VP. Electrocardiographic findings during extended clinical trials of fluvoxamine in depression: one years experience. *Pharmacopsychiatry*. 1995;28:253-256. doi:10.1055/s-2007-979612.
32. Rodriguez de la Torre B, Dreher J, Malevany J, et al. Serum levels and cardiovascular effects of tricyclicantidepressants and selective serotonin reuptake inhibitors in depressed patients. *Ther Drug Monit*. 2001;23:435-440.
33. Laird LK, Lydiard RB, Morton WA, et al. Cardiovascular effects of imipramine, fluvoxamine, and placebo in depressed outpatients. *J Clin Psychiatry*. 1993;54:224-228.
34. Hewer W, Rost W, Gattez WF. Cardiovascular effects of fluvoxamine and maprotiline in depressed patients. *Eur Arch Psychiatry Clin Neurosci*. 1995;246:1-6. doi:10.1007/BF02191808.
35. Luvox (fluvoxamine) [product information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2012.
36. Brzozowska A, Werner B. Observation of QTc prolongation in an adolescent girl during fluvoxamine pharmacotherapy. *J Child Adolesc Psychopharmacol*. 2009;19:591-592. doi:10.1089/cap.2008.0136.
37. Nelson JC, Lu Pritchett Y, Martynov O, Yu JY, Mallinckrodt CH, Detke MJ. The safety and tolerability of duloxetine compared with paroxetine and placebo: a pooled analysis of 4 clinical trials. *Prim Care Companion J Clin Psychiatry*. 2006;8:212-219.
38. Kuhs H, Rudolf GA. Cardiovascular effects of paroxetine. *Psychopharmacology*. 1990;102:379-382. doi:10.1007/BF02244107.
39. Edwards JG, Goldie A, Papayanni-Papasthatis S. Effect of paroxetine on the electrocardiogram. *Psychopharmacology*. 1989;97:96-98. doi:10.1007/BF00443420.
40. Yerangi VK, Pohl R, Jampala VC, Balon R, Ramesh C, Srinivasan K. Effects of nortriptyline and paroxetine on QT variability in patients with panic disorder. *Depress Anxiety*. 2000;11:126-130. doi:10.1002/(SICI)1520-6394(2000) 11:3<126::AID-DA7>3.0.CO;2-1.
41. Martin DE, Zussman BD, Everitt DE, Benincosa LJ, Etheredge RC, Jorkasky DK. Paroxetine does not affect the cardiac safety and pharmacokinetics of terfenadine in healthy adult men. *J Clin Psychopharmacol*. 1997;17:451-459.

42. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *J Clin Psychopharmacol*. 2013;3:3-10. doi:10.1097/JCP.0b013e31827c0314.
43. Lim KS, Jang IJ, Kim BH, et al. Changes in the QTc interval after administration of flecainide acetate, with and without coadministered paroxetine, in relation to cytochrome P450 2D6 genotype: data from an open-label, two-period, single-sequence crossover study in healthy Korean male subjects. *Clin Ther*. 2010;32:659-666. doi:10.1016/j. clinthera. 2010.04.002.
44. Paxil (paroxetine) [product information]. Research Triangle Park, NC: GlaxoSmithKline; 2013.
45. Guy S, Silke B. The electrocardiogram as a tool for therapeutic monitoring: a critical analysis. *J Clin Psychiatry*. 1990;51(suppl B):37-39.
46. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288:701-709. doi:10.1001/jama.288.6.701.
47. Wilens TE, Biederman J, March JS, et al. Absence of cardiovascular adverse effects of sertraline in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:573-577. doi:10.1097/00004583-199905000-00019.
48. Amin M, Lehmann H, Miriran J. A double-blind, placebo-controlled dose-finding study with sertraline. *Psychopharmacol Bull*. 1989;25:164-168.
49. Moeller O, Evers S, Deckert J, et al. The impact of ziprasidone in combination with sertraline on visually-evoked event-related potentials in depressed patients with psychotic features. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:1440-1443. doi:10.1016/j.pnpbp.2007.06.021.
50. Alderman J. Coadministration of sertraline with cisapride or pimozide: an open-label, nonrandomized examination of pharmacokinetics and corrected QT intervals in healthy adult volunteers. *Clin Ther*. 2005;27:1050-1063. doi:10.1016/j.clinthera.2005.07.013.
51. Hoehns JD, Fouts MM, Kelly MW, Tu KB. Sudden cardiac death with clozapine and sertraline combination. *Ann Pharmacother*. 2001;35:862-866. doi:10.1345/aph.16185.
52. Patane S, Marte F, Di Bella G. QT interval prolongation and torsade de pointes. *Int J Cardiol*. 2009;131:e51-e53. doi:10.1016/j.ijcard.2007.05.100.
53. Lynch DR, Washam JB, Newby LK. QT interval prolongation and torsades de pointes in a patient undergoing treatment with vorinostat: a case report and review of the literature. *Cardiol J*. 2012;19: 434-438.
54. Zoloft (sertraline) [product information]. New York, NY: Pfizer; 2012.
55. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA*. 2003;289:2120-2127. doi:10.1001/jama.289.16.2120.
56. Rajamani S, Eckhardt LL, Valdivia CR, et al. Drug-induced long QT syndrome: HERG K+ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine. *Br J Pharmacol*. 2006;149:481-489. doi:10.1038/sj.bjp.0706892.
57. Isbister GK, Bowe SJ, Dawson A, Whyte IM. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol*. 2004;42:277-285.
58. De Boer RA, van Dijk TH, Holman ND, van Melle JP. QT interval prolongation after sertraline overdose: a case report. *BMC Emerg Med*. 2005;5:5. doi:10.1186/1471-227X-5-5.
59. Poluzzi E, Raschi E, Moretti U, De Ponti F. Drug-induced *torsades de pointes*: data mining of the public version of the FDA Adverse Event Reporting System (AERS). *Pharmacoepidemiol Drug Saf*. 2009;18:512-518. doi: 10. 1002/pds.1746.
60. Zivin K, Pfeiffer PN, Bohnert ASB, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am J Psychiatry*. 2013;170:642-650. doi:10.1176/appi.ajp.2013.12030408.
61. Teter CJ, Kando JC, Wells BG. Major depressive disorder. In: Talbert RL, DiPiro JT, Matzke GR, Posey LM, Wells BG, Yee GC, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York, NY: McGraw-Hill; 2011:chap 77.
62. American Psychiatric Association. *Practice guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Publishing; 2010. doi:10.1176/appi.books.9780890423387.654001.