Meta-Analysis of Selective Serotonin Reuptake Inhibitor–Associated QTc Prolongation

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ABSTRACT

Objective: To evaluate the association between selective serotonin reuptake inhibitors (SSRIs) and corrected QT interval (QTc) prolongation via meta-analysis of prospective studies.

Data Sources: PubMed/MEDLINE database (January 1, 1975–August 15, 2012), with additional reports identified using hand searches of reference lists of relevant articles. Key words searched were *QT, torsades de pointes,* and *sudden cardiac death,* combined with *antidepressants, citalopram, escitalopram, fluoxetine, sertraline, paroxetine,* and *fluvoxamine.* English-, Spanish-, and German-language articles were included.

Study Selection: Two reviewers independently identified prospective controlled studies in adults that reported data related to QTc intervals prior to and following treatment with SSRIs.

Data Extraction and Synthesis: Three reviewers independently extracted study-level data including population characteristics, method of QTc measurement and treatment and outcome data. Two independent reviewers critiqued study quality. Publication bias was assessed visually using a funnel plot and quantitatively. Heterogeneity was measured using Cochran *Q* statistic.

Results: Sixteen articles (with 25 distinct data subsets) involving 4,292 patients were included. SSRIs were associated with a dose-dependent increase in QTc interval compared to placebo (+6.10 milliseconds; 95% CI, 3.47–8.73; $P < .001$). Tricyclic antidepressants (TCAs) were associated with a significantly greater QTc increase than SSRIs (TCA prolongation, 7.05 milliseconds; 95% CI, 3.84–10.27 greater than SSRIs; $P < .001$). With respect to specific SSRI agents, citalopram was associated with significantly greater QTc prolongation than sertraline, paroxetine, and fluvoxamine.

Conclusions: SSRIs were associated with a modest but statistically significant increase in the QTc interval, although to a lesser extent than TCAs; this finding was not limited to any single study. Citalopram was associated with more QTc prolongation than most other SSRIs.

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QT interval prolongation is a risk factor for serious adverse events, including torsades de pointes, a potentially fatal ventricular arrhythmia.[1,2] Because the QT interval is inversely proportional to heart rate, it is typically corrected for heart rate (QTc), with a normal QTc interval defined as less than 460 milliseconds for women and less than 450 milliseconds for men.[3] Medications are among the many risk factors for QTc prolongation, and it is estimated that up to 3% of all prescriptions are for medications that may prolong the QTc interval.[4]

Psychiatrists are generally familiar with concerns related to prolongation of the QTc interval in the setting of antipsychotic use. Over the years, several antipsychotics, including intravenous haloperidol and, more recently, ziprasidone, have been linked in varying degrees to QTc prolongation, torsades de pointes, and/or sudden cardiac death. Older antidepressants, such as tricyclic antidepressants (TCAs), have also been linked to prolongation of the QTc interval, albeit through a distinct mechanism. Selective serotonin reuptake inhibitors (SSRIs), on the other hand, have been the mainstay of depression treatment over the past 25 years and have safer cardiac profiles than TCAs.[5,6] Recently, however, the cardiac safety of SSRIs with regard to QTc prolongation has been called into question. Case reports have appeared linking all 6 of the SSRIs to QTc prolongation, and to torsades de pointes in some instances, but these reports are sparse and anecdotal.[7] More systematic evaluations, however, have suggested that some SSRIs, particularly citalopram, may have a predictable QTc-prolonging effect.[7] These data culminated in recommendations by the US Food and Drug Administration (FDA) in August 2011 and March 2012 to limit citalopram to dosages of 40 mg daily or less in patients (and 20 mg daily or less in those older than 60 years and/or with hepatic impairment) because of the increased risk of QTc prolongation at higher doses.[8,9] Although other prospective studies examining the effect of SSRIs on the QTc interval have been conducted over the past 25 years, the FDA recommendation was based on a single study involving citalopram. Despite the substantial clinical implications of these connections, no prior work has pooled data from previous clinical trials and systematically evaluated the QTc-prolonging effect of SSRIs using a meta-analytic approach.

We undertook a systematic review of the literature and meta-analysis to more thoroughly characterize the effect of SSRIs on QTc. Specifically, we examined whether SSRIs increased the QTc interval as compared to placebo, whether SSRIs increased the QTc interval as compared to TCAs, and whether citalopram had a greater impact on the QTc interval than other individual SSRIs.

METHOD

The methods for conducting and reporting this meta-analysis follow the Quality of Reporting of Meta-Analyses (QUOROM) and

Clinical Points

- Selective serotonin reuptake inhibitors (SSRIs) appear to cause prolongation of the QTc by about 6 milliseconds as compared to placebo, and tricyclic antidepressants appear to prolong the QTc interval by an additional 7 milliseconds as compared to placebo.
- Among the SSRIs, it appears that citalopram is associated with significantly greater QTc prolongation than many other agents.
- It would be prudent to choose an SSRI other than citalopram as first-line treatment for depression in patients demonstrating risk factors for QTc prolongation.

Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[10,11]

Search Strategy and Study Selection

Study investigators retrieved potential studies based on a literature search of articles from January 1975 through August 15, 2012, using the PubMed/MEDLINE database to identify studies reporting data on QTc interval in the setting of SSRI use. This ensured that searches spanned from the earliest reports on SSRIs (fluoxetine, 1975) to the present. We used the following search terms: *QT*, *torsades de pointes*, and *sudden cardiac death* combined with *antidepressants*, *citalopram*, *escitalopram*, *fluoxetine*, *sertraline*, *paroxetine*, and *fluvoxamine*, for a total of 21 separate searches. To obtain additional relevant reports, we hand searched bibliographies of retrieved studies, contacted expert investigators in the field, and reviewed pertinent websites (eg, the FDA website).

Study Selection

Two reviewers (S.R.B. and C.M.C.) performed independent study selection, with discrepancies resolved through discussion and with the input of the senior author (J.C.H.). Open-label and randomized controlled prospective studies were included in the review if they reported QTc data prior to and following administration of SSRIs. Studies were excluded if they involved a retrospective design, did not specify the SSRI used, did not provide specific data on QTc (or data that could be used to calculate QTc, such as QT interval and RR interval) in the active and control groups, did not report human data, or were published in languages other than English, German, or Spanish. Case series and reports were excluded, as were editorials and review articles. For trials reported in more than 1 publication, we obtained data from the publication with the most complete data and used others for clarification.

Data Extraction

A total of 16 articles, with 25 distinct subsets of data (Figure 1 and Table 1), met inclusion criteria. Full text was obtained for all articles. For unpublished data, we also contacted pharmaceutical companies associated with the agent/data. If specific data were not available, study authors were contacted by e-mail. Three reviewers (S.R.B., W.J.K., and C.M.C.) independently coded data on each study (Table 1). Information on the QTc interval was collected for the active and control medications in each of the studies. The total number of disagreements in coding across the 25 identified studies/subsets was 20; differences were reconciled with the help of the senior author (J.C.H.) in all cases.

QTc values were included in the reports of 21 subsets. In 4 subsets, the QTc was calculated by W.J.K. using the Bazett formula (QTc = reported QT/$\sqrt{}$ RR interval). The standard deviation (SD) or other measurements of interval variability reported in the study were not available for 12 of the 25 subsets. For these 12 subsets, the SD of the primary end point (defined below) was estimated as follows: a meta-analysis was performed to calculate the weighted variance of the 13 remaining subsets with available SD or standard error of the mean (SEM). The weighted variance obtained by the meta-analysis of the 13 subsets as described above was then used to estimate the variance (and the SD) of the 12 subsets with missing values for variance (and SD and SEM), using the square root of N of each study.

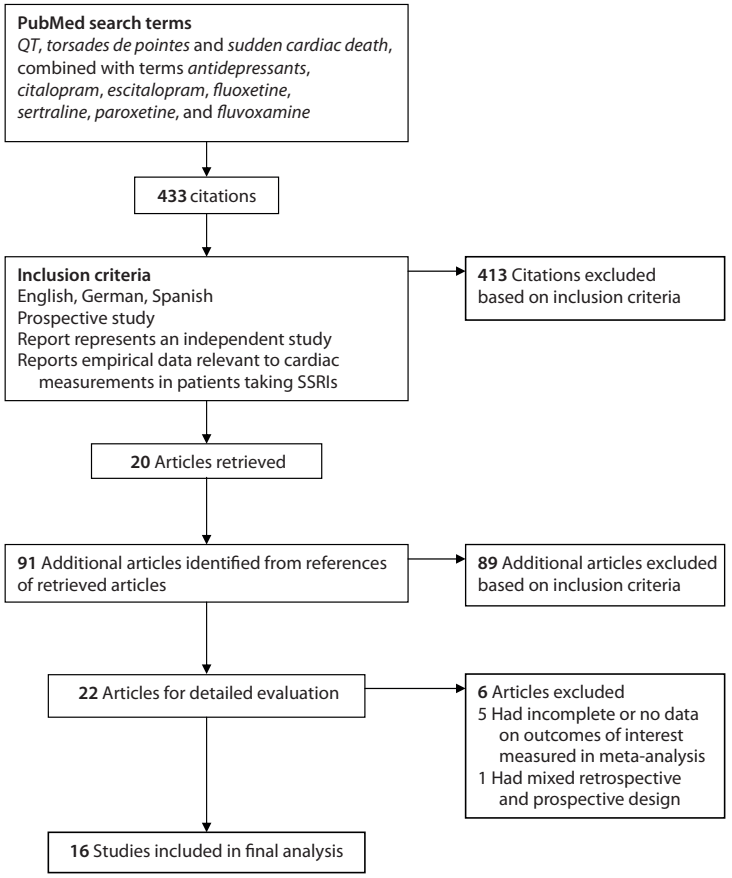
Methodological Study Assessment

Study quality was independently assessed by S.R.B. and C.M.C. using a 7-item quality checklist that utilized relevant items from Downs and Black[27] regarding methodological study quality assessment. The checklist assigned scores in each category to sum to a total (7–21) quality score. The items used in the checklist, with scores, were blinding (none [1], single-blind [2], double-blind [3]), randomization (none [1], randomization attempted but suboptimal [2], successful [3]), dosing of SSRI (maximal study dose subtherapeutic [1], maximal study dose at low end of therapeutic range [2], maximal study dose at high end of therapeutic range [3]), duration of SSRI administration (< 1 week [1], 1–3 weeks [2], > 3 weeks [3]), sample size (< 50 [1], 50–127 [2], > 127 [3]), nature of sample (nondepressed healthy persons [1], medically healthy patients with psychiatric illness [2], cardiac patients with psychiatric illness [3]), and method of QTc calculation (not calculated by authors or not stated [1], calculated by authors using Bazett formula [2], or calculated by authors using linear correction equation [3]). All disagreements related to study quality (intraclass correlation coefficient [κ] between raters [S.R.B. and C.M.C.] = 0.96) were resolved by discussion and review via consensus as above.

Statistical Analyses

The impact of SSRI and control (ie, placebo or TCA) medications on the QTc was determined for all main analyses and subanalyses. All subsets, including crossover studies, were conservatively considered as independent samples, given the use of unpaired comparisons. The *effect on QTc* of the active or control medication was defined as the difference in milliseconds between the QTc measurement at the final visit and the QTc measurement at the baseline visit.

Figure 1. CONSORT Diagram of Data Extraction



Abbreviation: SSRI = selective serotonin reuptake inhibitor.

The *primary end point* of the analyses was the difference between the QTc during administration of the active medication and the QTc at baseline or during administration of the control medication.

A total of 3 meta-analyses were performed, using random-effects models:

1. Comparison of QTc effect between SSRI and placebo for placebo-controlled trials examining QTc before and after medication initiation.
2. Comparison of QTc effect between SSRI and TCA for TCA-controlled trials examining QTc before and after medication initiation.
3. Examination of individual SSRI agents' effect on QTc in placebo-controlled trials: specifically, QTc effects for each SSRI versus placebo. In addition, given the conjecture that citalopram causes more QTc prolongation, the QTc effects of citalopram were compared with effects for each of the other SSRIs in a pairwise fashion.

The random-effects meta-analysis weights the studies by their inverse variance, modeled as the sum of the within-study and between-study variances. We did not perform additional weighting of the studies by study quality, and such approaches may introduce additional bias.[28]

We performed additional analyses to further explore other factors that could serve as moderator variables in the links between medications and QTc. Meta-regressions of the random-effects meta-analyses were performed with respect to adjusted dose of the active drug (SSRI), adjusted dose of the control drug (TCA), and "dose" of placebo; we also completed meta-regressions with respect to patient age and duration of treatment. Finally, to assess the effect of study design, additional meta-analyses were performed considering only the crossover and only the parallel design subsets.

Heterogeneity of effect size was assessed using the Cochran *Q* statistic.[29] Publication bias was assessed visually using a funnel plot and quantitatively using an adjusted rank correlation test and a regression procedure to measure funnel plot asymmetry. The trim-and-fill method by Duval and Tweedie[30] was used to adjust for potential publication bias. This method assesses asymmetry in the funnel plot, imputes the number of suspected missing studies, and recalculates the adjusted effect size estimate. The adjusted result can be used as a sensitivity analysis to indicate the extent to which publication bias may affect the pooled estimate. Fail-safe N (describing the number of additional studies needed to bring the $P > .05$)[31] and Orwin fail-safe N (describing the number of studies needed to decrease the observed delta of QTc by 10-fold)[32] were also calculated.

For all analyses, a 2-tailed $P < .05$ was used to determine statistical significance. Statistical analyses were performed with JMP (version 9.0, SAS Institute, Cary, North Carolina) and Comprehensive Meta Analysis (version 2.2, Biostat, Englewood, New Jersey) statistical software.

RESULTS

Study Identification and Selection

Figure 1 illustrates the study selection and retrieval strategy. Reviewers identified 433 unique citations via literature search, and an additional 91 citations were added following supplementary hand searches of bibliographies, for a total of 524 citations. Five hundred two studies were excluded after title and abstract screening. The remaining 22 studies were retrieved in full for detailed evaluation. Five of these were excluded because they did not report QTc interval prior to and following treatment with SSRI,[33–37] and 1 was excluded because it included only uncorrected QT values and listed no heart rate or RR interval data to allow estimation of QTc.[38] Sixteen articles (Table 1) were selected that separately reported outcome data regarding QTc interval prior to and following antidepressant therapy.

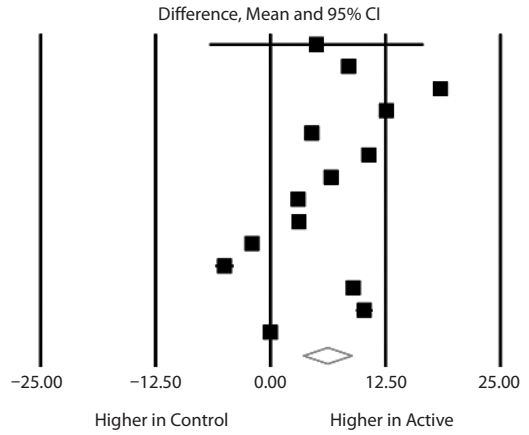
Table 1. Characteristics of Studies Included in the Meta-Analysis

Source	Active Medication, n	Total, N	Active Medication	Control Medication	Population	Study Type	Design	Blinding	Duration, d	Active Medication Dose, Range, mg	Age, y	Method of QT Measurement	Method of QTc Calculation	Active Medication Group QTc, ms		Control Group QTc, ms		Quality Rating
														Baseline Visit	Final Visit	Baseline Visit	Final Visit	
Robinson and Doogan, 1982[12]	27	27	Fluvoxamine	Placebo	Healthy subjects	Crossover	RCT	DB	9	50–300	NA	Single-lead 24-h Holter ECG	Bazett	414	412	414	420	15
Upward et al, 1988 (subset 1)[13]	13	27	Fluoxetine	Amitriptyline (TCA)	Depression, no cardiac disease	Parallel	RCT	DB	7	40	42.5	High-speed ECG	Bazett	401.0	407.0	418.0	411.0	17
Upward et al, 1988 (subset 2)[13]	13	27							21	60–80	42.5			401.0	411.0	418.0	424.0	
Baker et al, 1997 (subset 1)[14]	20	40	Fluoxetine	Doxepin	Depression, no cardiac disease	Parallel	RCT	DB	14	20–60	42.5	12-lead ECG	Bazett	403.0	404.0	408.0	416.0	17
Baker et al, 1997 (subset 2)[14]	20	40							28	20–60	42.5			403.0	403.0	408.0	421.0	
Baker et al, 1997 (subset 3)[14]	20	40							42	20–60	42.5			403.0	403.0	408.0	416.0	
Roose et al, 1998[15]	27	87	Fluoxetine	Placebo	Depression and cardiac disease	Parallel	RCT	Open	14 (fluoxetine); 21 (nortriptyline)	20	70.7	12-lead ECG	Bazett	441.0	450.0			14
Strik et al, 2000[16]	27	54	Fluoxetine	Placebo	Depression and cardiac disease	Parallel	RCT	DB	175	20–60	56.4	12-lead ECG	By authors	417.0	417.0	414.0	414.0	18
Edwards et al, 1989[17]	11	20	Paroxetine	Placebo	Depression, no cardiac disease	Parallel	RCT	Blinded ECG	28	30	39.8	12-lead ECG	Bazett	407.0	404.0	408.0	400.0	16
Kuhs et al, 1990[18]	20	40	Paroxetine	Amitriptyline	Depression, no cardiac disease	Parallel	RCT	DB	42	30	41.0	12-lead ECG	Bazett	418.0	414.0	416.0	431.0	16
Roose et al, 1998 (subset 1)[19]	41	81	Paroxetine	Nortriptyline	Depression and cardiac disease	Parallel	RCT	DB	14	20–40	58.0	12-lead ECG	By authors	420.0	417.0	427.0	434.0	18
Roose et al, 1998 (subset 2)[19]	41	81							42	20–40	58.0			420.0	419.0	427.0	416.0	
Yeragani et al, 2000[20]	16	29	Paroxetine	Nortriptyline	Panic disorder, no cardiac disease	Parallel	CT	Open	105 (paroxetine); 77 (nortriptyline)	20	34.1	Single-lead ECG	By authors	459.5	438.7	459.0	466.5	12
Nelson et al, 2006[21]	359	1466	Paroxetine	Placebo	Depression, no cardiac disease	Parallel	RCT	DB	56	20	43.2	12-lead ECG	By authors	405.7	404.7	405.5	406.5	17
Fisch et al, 1992 (subset 1)[22]	459	703	Sertraline	Amitriptyline	Depression, no cardiac disease	Parallel	RCT	DB	28–56	50–400	40.2	12-lead ECG	By authors	388.1	388.5	386.5	387.1	18
Fisch et al, 1992 (subset 2)[22]	273	479							56	50–200	51.7			388.1	388.5	391.9	399.9	
Glassman et al, 2002[23]	186	369	Sertraline	Placebo	Depression and cardiac disease	Parallel	RCT	DB	112	50–200	57.2	12-lead ECG	Bazett	420.0	418.0	424.0	419.0	20
Slavicek et al, 1998[24]	30	52	Citalopram	Placebo	Depression, no cardiac disease	Parallel	CT	Open	28–35	20–60	41.0	Body surface map	By authors					12
Lesperance et al, 2007[25]	142	284	Citalopram	Placebo	Depression and cardiac disease	Parallel	RCT	DB	84	20–40	58.2	12-lead ECG	Bazett	416.3	418.1	416.4	415.1	19
FDA citalopram (subset 1)[8]	120	120	Citalopram	Placebo	Healthy subjects	Crossover	RCT	DB	9	20	31.5	12-lead ECG	Individual correction					19
FDA citalopram (subset 2)[8]	120	120							9	40	31.5							
FDA citalopram (subset 3)[8]	120	120							22	60	31.5							
FDA escitalopram (subset 1)[26]	120	120	Escitalopram	Placebo	Healthy subjects	Crossover	RCT	DB	9	10	27.3	12-lead ECG	Individual correction					19
FDA escitalopram (subset 2)[26]	120	120							9	20								
FDA escitalopram (subset 3)[26]	120	120							22	30								

Abbreviations: CT = controlled trial, DB = double blind, ECG = electrocardiogram, NA = not available, RCT = randomized controlled trial, TCA = tricyclic antidepressant.

Figure 2. Effects of Selective Serotonin Reuptake Inhibitors on QTc When Compared to Placebo

Study	N	Mean difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Edwards et al[17]	20	5.00	5.96	−6.69	16.69	.4019
FDA-1[8]	120	8.50	0.09	8.33	8.67	< .001
FDA-2[8]	120	18.50	0.09	18.33	18.67	< .001
FDA-3 (modeled)[8]	120	12.60	0.09	12.43	12.77	< .001
FDA-4[26]	120	4.50	0.09	4.33	4.67	< .001
FDA-5[26]	120	10.70	0.09	10.53	10.87	< .001
FDA-6 (modeled)[26]	120	6.60	0.09	6.43	6.77	< .001
Glassman et al[23]	369	3.00	0.02	2.95	3.05	< .001
Lesperance et al[25]	284	3.10	0.02	3.06	3.14	< .001
Nelson et al[21]	1,466	−2.00	0.00	−2.00	−2.00	< .001
Robinson and Doogan[12]	27	−5.00	0.53	−6.05	−3.95	< .001
Roose et al[15]	87	9.00	0.38	8.26	9.74	< .001
Slavicek et al[24]	52	10.20	0.48	9.25	11.15	< .001
Strik et al[16]	54	0.00	0.31	−0.61	0.61	1.0000
Total	**3,079**	**6.10**	**1.34**	**3.47**	**8.73**	**< .001**



Abbreviations: FDA = US Food and Drug Administration, QTc = corrected QT interval.

From these remaining 16 articles, we defined 25 relevant subsets for analysis (Table 1). Two studies of citalopram and escitalopram commissioned by the FDA[8,39] accounted for 6 subsets, 1 study[14] for 3 subsets, and 3 studies[13,19,22] for 2 subsets each. With respect to the FDA studies of citalopram and escitalopram, low (20-mg citalopram, 10-mg escitalopram) and high (60-mg citalopram, 30-mg escitalopram) doses were studied without investigation of effects at intermediate dose; the QTc effects of the intermediate doses (40-mg citalopram, 20-mg escitalopram) were estimated by those studies' authors, and these values were used as a separate, third subset for each study.[8,39] Overall, study quality was moderate (mean score = 16.7 of 21 on the 7-item checklist; range, 12–20), with most studies (10/16) scoring 17 or above.

Study Characteristics

All studies ultimately used in the meta-analysis were published in English. Sample size ranged from 20 to 1,466 for a total of 4,292 subjects. Twenty-one subsets were double-blind, 3 were open, and 1 had a blinded electrocardiogram reading. Fourteen subsets pertained to placebo-controlled trials, and the remaining 11 pertained to TCA-controlled trials. Among the trials classified as placebo-controlled, 1 was an open-label trial in which no medication, instead of true placebo, was used in the control group.[15]

Seven subsets were studies with crossover design (all placebo-controlled), and the remaining 18 subsets were parallel design (7 placebo-controlled, 11 TCA-controlled). The duration of the studies ranged from 7 to 175 days, with a mean ± SD of 41.0 ± 45.3 days. The mean ± SD age of subjects was 42.5 ± 13.0 years. The mean ± SD adjusted SSRI dose was 58.6% ± 31.3% of the maximum FDA-approved dose, and the mean ± SD adjusted TCA dose was 80.6% ± 26.1% of the maximum FDA-approved dose.

All SSRIs approved for use in the United States (paroxetine, citalopram, escitalopram, sertraline, fluvoxamine, and fluoxetine) were included in at least 1 trial, allowing comparative analysis to be performed between citalopram and all other available SSRIs. Five controlled trials prospectively examined the effect of paroxetine, 4 randomized controlled trials (RCTs) (3 double-blind and 1 open-label) examined the effects of fluoxetine, and 3 studies (2 RCTs and 1 open-label) examined the effects of citalopram on the QTc interval; fewer studies existed for the other SSRIs (Table 1).

Analysis 1: QTc Effect in Trials of SSRI Versus Placebo (14 total subsets; n = 2,599)

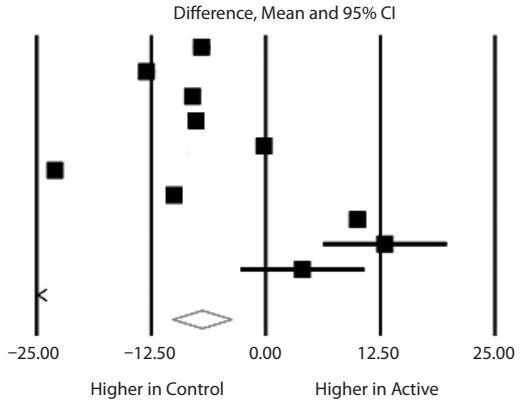
Compared to placebo, SSRIs were associated with a greater increase in QTc by 6.10 milliseconds (95% CI, 3.47–8.73; Figure 2). On sensitivity analyses by trial design, in the 7 placebo-controlled parallel design subsets, SSRIs resulted in longer QTc by 3.91 milliseconds (95% CI, 1.09–6.73; $P < .0001$). There was significant inhomogeneity in the crossover trials (P for interaction = .03), but not in the parallel design trials ($P = .17$).

On a meta-regression of the primary end point by adjusted dose of the SSRI (percentage of FDA maximum dose at the time of the study), a positive relationship between the primary end point and the adjusted SSRI dose was observed, such that for an adjusted dose increase of 1% of the FDA maximum dose, there was a 0.1948 (95% CI, 0.1938–0.1957; $P < .0001$) millisecond increase in QTc. As expected, the slope in the meta-regression of placebo-controlled studies was not significantly different from 0, suggesting that there was no change in QTc effect with different "doses" of placebo. Significant effects were not observed when duration of treatment and average patient age in each study were used as moderator variables in additional meta-regressions.

Finally, a meta-analysis of the 7 placebo-controlled studies was performed 7 times by omitting 1 study at a time in order to investigate whether 1 study determined the overall effect. Across these analyses, the point estimate of the QTc difference varied from 6.36 milliseconds (95% CI, 3.65 to 9.07; $P < .0001$) to 10.23 milliseconds (95% CI, 6.25 to 14.21; $P < .0001$), suggesting that the observed effect

Figure 3. Effects of Selective Serotonin Reuptake Inhibitors on QTc When Compared to Tricyclic Antidepressants

Study	N	Mean difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Baker et al[14] (subset 1)	40	−7.00	0.52	−8.01	−5.99	< .001
Baker et al[14] (subset 2)	40	−13.00	0.49	−13.96	−12.04	< .001
Baker et al[14] (subset 3)	40	−8.00	0.47	−8.92	−7.08	< .001
Fisch et al[22] (subset 1)	703	−7.60	0.01	−7.61	−7.59	< .001
Fisch et al[22] (subset 2)	479	−0.20	0.00	−0.21	−0.19	< .001
Kuhs et al[18]	40	−23.00	0.44	−23.86	−22.14	< .001
Roose et al[19] (subset 1)	81	−10.00	0.11	−10.22	−9.78	< .001
Roose et al[19] (subset 2)	81	10.00	0.11	9.79	10.21	< .001
Upward et al[13] (subset 1)	27	13.00	3.47	6.20	19.80	< .001
Upward et al[13] (subset 2)	27	4.00	3.47	−2.81	10.81	.2494
Yeragani et al[20]	29	−28.30	1.61	−31.45	−25.15	< .001
Total	**1,587**	**−7.05**	**1.64**	**−10.27**	**−3.84**	**< .001**



Abbreviation: QTc = corrected QT interval.

on the QTc interval was not related to any single study. A prolongation of QTc was observed in all 7 analyses.

Analysis 2: QTc Effect in Trials of SSRIs Versus TCA (11 subsets; n = 1,399)

In the 11 subsets comparing TCAs to SSRIs (all parallel-design trials), SSRIs resulted in shorter QTc by 7.05 milliseconds (95% CI, 3.84–10.27; $P < .001$; Figure 3); there was no overlap of the CIs between SSRI versus placebo and SSRI versus TCAs. There was significant inhomogeneity ($P < .001$) within these TCA-controlled trials, by individual TCA agent used.

A negative slope was observed in the meta-regression of the primary end point by adjusted dose of the TCA, suggesting that higher doses of TCAs were associated with a larger QTc difference in these studies. An inverse relationship between the primary end point (in ln scale) and the adjusted TCA dose was observed (slope = −0.00182; 95% CI, −0.00004 to −0.00189; $P < .0001$).

Meta-analysis of TCA-based trials to assess whether 1 trial led to overall effect was performed 11 times by sequentially omitting 1 study at a time. Removing the study by Fisch and Knoebel[22] resulted in a significantly smaller decrease in QTc change (−4.28 milliseconds; 95% CI, −7.34 to −1.23). However, the effect remained statistically significant ($P = .0060$).

Analysis 3: Effects of Individual SSRIs on QTc

Citalopram (10.58 milliseconds; 95% CI, 3.93 to 17.23; $P = .0018$), escitalopram (7.27 milliseconds; 95% CI, 3.78 to 10.83; $P = .0001$), and sertraline (3.00 milliseconds; 95% CI, 2.95 to 3.05; $P < .0001$) had statistically greater QTc prolongation than placebo; fluoxetine (4.50 milliseconds; 95% CI, −4.32 to 13.32; $P = .31$) and paroxetine (−1.04 milliseconds; 95% CI, −5.76 to 3.68; $P = .67$) were not significantly associated with QTc prolongation (Figure 4). Fluvoxamine, studied in only a single placebo-controlled trial, was associated with a significant shortening of QTc (−5.00 milliseconds; 95% CI, −6.05 to −3.95; $P < .0001$).

Citalopram caused significantly greater QTc prolongation than sertraline, paroxetine, and fluvoxamine, as evidenced by nonoverlap of the 95% CI for these agents in comparing their QTc effect versus placebo; differences in QTc effect were not significant between citalopram and escitalopram or between citalopram and fluoxetine.

Publication Bias

A funnel plot was constructed to examine publication bias when all studies were considered. The plot indicated an asymmetry with 6 studies on the right not balanced by studies on the left. To achieve balance, we imputed 6 compensatory studies in order to balance the funnel plot. The result of the analysis was statistically significant, with the point estimate being −1.914 milliseconds (95% CI, −1.918 to −1.911) before the addition of the new 6 studies. With the addition of the 6 imputed studies, the point estimate changed to −1.941 milliseconds (95% CI, −1.938 to −1.944), and the effect remained statistically significant. Duval fail-safe N describing the number of additional studies that would bring the *P* value to more than .05 is 4,844 neutral studies. Orwin fail-safe N to decrease the observed delta of the QTc 10-fold is 226.

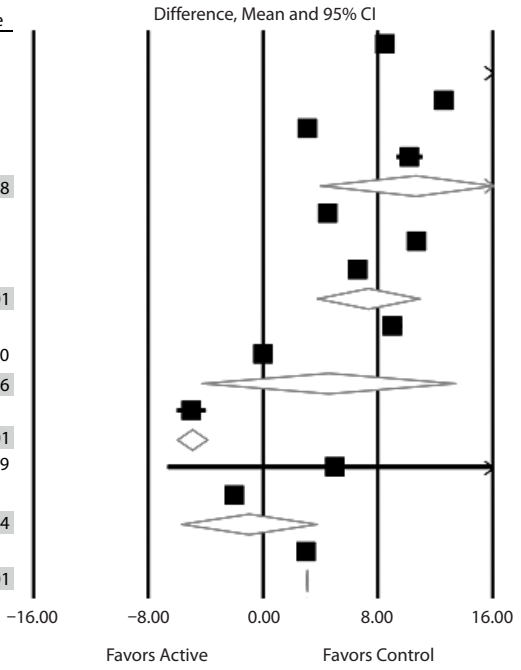
Similarly, a funnel plot was constructed to examine publication bias when only placebo-controlled studies were considered. The plot was symmetrical, and there was no need to impute studies to balance it. Duval fail-safe N was 9,055 neutral studies; Orwin fail-safe N was 64.

DISCUSSION

We found that SSRIs, as a class, were linked with prolongation of the QTc interval by approximately 6 milliseconds when compared to placebo, and that such QTc prolongation was dose dependent. Selective serotonin reuptake inhibitors, similarly to most other QTc-prolonging medications, are thought to cause QTc prolongation via direct blockade of rapid potassium delayed rectifier current (Ikr), the delayed potassium rectifier current, encoded by the human ether-a-go-go-related gene (hERG).[1] In animal

Figure 4. Effects of Individual Selective Serotonin Reuptake Inhibitors (SSRIs) on QTc When Compared to Placebo

SSRI	Study	N	Mean Difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Citalopram	FDA-1[8]	120	8.50	0.09	8.33	8.67	< .001
Citalopram	FDA-2[8]	120	18.50	0.09	18.33	18.67	< .001
Citalopram	FDA-3 (modeled)[8]	120	12.60	0.09	12.43	12.77	< .001
Citalopram	Lesperance et al[25]	284	3.10	0.02	3.06	3.14	< .001
Citalopram	Slavicek et al[24]	52	10.20	0.48	9.25	11.15	< .001
Citalopram		696	10.58	3.39	3.93	17.23	.0018
Escitalopram	FDA-4[26]	120	4.50	0.09	4.33	4.67	< .001
Escitalopram	FDA-5[26]	120	10.70	0.09	10.53	10.83	< .001
Escitalopram	FDA-6 (modeled)[26]	120	6.60	0.09	6.43	9.74	< .001
Escitalopram		360	7.27	1.82	3.78	10.83	< .0001
Fluoxetine	Roose et al[19]	81	9.00	0.38	8.26	13.32	< .001
Fluoxetine	Strik et al[16]	54	0.00	0.31	−0.61	−3.95	1.0000
Fluoxetine		135	4.50	4.50	−4.32	13.32	.3176
Fluvoxamine	Robinson ad Doogan[12]	27	−5.00	0.53	−6.05	16.69	< .001
Fluvoxamine		*27*	−5.00	0.53	−6.05	−3.95	< .0001
Paroxetine	Edwards et al[17]	20	5.00	5.96	−6.69	3.68	.4019
Paroxetine	Nelson et al[21]	1,466	−2.00	0.00	−2.00	3.05	< .001
Paroxetine		1,486	−1.04	2.41	−5.76	3.68	.6654
Sertraline	Glassman et al[23]	369	3.00	0.02	2.95		< .001
Sertraline		369	3.00	0.02	2.95	3.05	< .0001



Abbreviations: FDA = US Food and Drug Administration, QTc = corrected QT interval.

models, citalopram, fluoxetine, sertraline, and fluvoxamine have been demonstrated to be Ikr/hERG inhibitors.[40–42]

Of note, the 6-millisecond mean prolongation found in our analysis is a small increase compared to that produced by most medications that have been clearly linked with QTc prolongation. Medications such as thioridazine, sotalol, and dofetilide have been associated with mean QTc increases of 30–40 milliseconds.[39,43–45] Ziprasidone, a drug that saw its FDA approval held for many years due to concerns about QTc interval prolongation, and iloperidone, a newer atypical antipsychotic, have been associated with QTc prolongation of at least 10 milliseconds.[46] Nonetheless, some noncardiovascular drugs that have been withdrawn from the market cause an increase in the QTc interval of only 5–10 milliseconds.[47]

Our results also suggest that TCAs prolong the QTc to a greater extent than SSRIs by a factor of more than 2, consistent with previous reports that TCAs carry greater cardiac risk.[5,6] Tricyclic antidepressants have traditionally been thought to cause QTc prolongation primarily through sodium and calcium channel blockade, and some TCAs may also block Ikr.[48,49] This dual mechanism of QTc prolongation may explain the more significant effect seen in our study.

Among individual SSRIs, citalopram appears to prolong the QTc to a greater extent than several other SSRIs. The literature in this regard is complex, with conflicting findings: citalopram has been implicated in 12 case reports of QTc prolongation, more than any other antidepressant in its class, and 5 cases reported prolongation at therapeutic doses.[7] A recent cross-sectional study examining electronic health records also concluded that citalopram and escitalopram, but not other SSRIs, were associated with modest QTc prolongation.[50] In contrast, however, several retrospective studies involving thousands of patients have demonstrated no QTc prolongation with citalopram.[34,51,52] Citalopram may have greater effects on QTc than other SSRIs via its metabolite didesmethylcitalopram[53] linked to impaired ventricular repolarization. Although didesmethylcitalopram is a minor metabolite in most humans, 2% of the general population are cytochrome P450 2D6 ultrarapid metabolizers, and thus could have higher concentrations.[54] Among other individual agents, escitalopram seems to have a dose-dependent, QTc-prolonging effect that was less but not significantly different from citalopram; the effects of escitalopram on Ikr or other repolarization currents are not known.

From a practical standpoint, there does not appear to be clear evidence to recommend caution or additional monitoring when using SSRIs other than citalopram in the general population. The modest overall QTc prolongation associated with SSRIs would be clinically insignificant for most patients, especially those with no other risk factors for torsades de pointes. QTc interval prolongation has a graded relationship to the risk of cardiac mortality and sudden death (presumably related to torsades de pointes in many cases), although the risk of sudden death, at the individual level, remains low.[1,2] A careful risk-benefit analysis that considers illness severity and other risk factors for QTc prolongation and torsades de pointes remains the best approach for determining whether to treat a given individual with a

medication that might cause a modest prolongation of the QTc interval.

The finding that citalopram might prolong the QTc to a greater extent than do other SSRIs may warrant caution and consideration of alternative agents in populations with QTc prolongation at baseline or with other torsades de pointes risk factors. The FDA continues to recommend that citalopram dosing be limited to 40 mg due to the risk of QTc prolongation. Although this recommendation may be overly conservative given the relatively low risk of modest QTc prolongation to most patients, our findings do support careful risk-benefit analysis. Sertraline, despite demonstrating a statistically significant QTc prolongation of 3 milliseconds in this meta-analysis, has been found to be safe for use in patients with preexisting cardiac disease.[23,55] Paroxetine or fluoxetine may also be reasonable alternatives, given their lack of QTc prolongation in this analysis. On the other hand, if there is a clinically compelling reason to use citalopram (eg, prior response and failure of other agents) in patients at elevated risk for torsades de pointes, such use may be warranted with increased monitoring.

This meta-analysis had several limitations. It was based on a moderate number of studies, which limited overall power as well as our ability to perform in-depth sensitivity analyses, and many of the studies examined were of moderate quality. A few studies used pooled data, and data for individual trials in those studies were not available. Further, patient-level data were not available for any of the studies. The forest plots comparing different SSRIs did not consider the relative doses of the agents studied, and the comparative analysis of individual agents was limited by the relative paucity of studies, particularly for fluvoxamine and escitalopram.

In conclusion, this first meta-analysis of these relationships found that SSRIs were associated with a small but statistically significant prolongation of the QTc. This risk was less than half of that seen with TCAs, and such prolongation appears to be largely confined to citalopram and escitalopram, which may drive the class effect. These findings were not limited to any individual trial and confirm the relatively modest QTc effects of SSRIs in a large number of patients. Prospective studies are warranted to further clarify the impact of these agents and to guide the FDA on further advisories regarding the risk of QTc prolongation with SSRIs.

Drug names: citalopram (Celexa and others), dofetilide (Tikosyn), doxepin (Silenor, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), iloperidone (Fanapt), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), sotalol (Betapace, Sorine, and others), ziprasidone (Geodon and others).

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