QT Interval Prolongation in Users of Selective Serotonin Reuptake Inhibitors in an Elderly Surgical Population: A Cross-Sectional Study

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ABSTRACT

Objective: To investigate the association between the use of a selective serotonin reuptake inhibitor (SSRI) and the occurrence of QT interval prolongation in an elderly surgical population.

Method: A cross-sectional study was conducted among patients (> 60 years) scheduled for outpatient preanesthesia evaluation in the period 2007 until 2012. The index group included elderly users of an SSRI. The reference group of nonusers of antidepressants was matched to the index group on sex and year of scheduled surgery (ratio, 1:1). The primary outcome was the occurrence of QT interval prolongation shown on electrocardiogram. The QT interval was corrected for heart rate (QTc interval). The secondary outcome was the duration of the QTc interval. The outcomes were adjusted for confounding by using regression techniques.

Results: The index and reference groups included 397 users of an SSRI and 397 nonusers, respectively. QTc interval prolongation occurred in 25 (6%) and 19 (5%) index and reference patients, respectively. After adjustment for confounding, users of an SSRI did not have a higher risk for QTc interval prolongation compared to nonusers: OR = 1.1 (95% CI, 0.5 to 2.0). The adjusted mean QTc interval length in users of an SSRI and nonusers was comparable (difference of 1.5 milliseconds [95% CI, −1.8 to 4.8]). Use of the most frequently used SSRIs citalopram and paroxetine was not associated with a higher risk of QTc interval prolongation nor with lengthening of the QTc interval duration.

Conclusions: The use of an SSRI by elderly surgical patients was not associated with the occurrence of QT interval prolongation.

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Antidepressants are used in the treatment of depressive disorders and several other conditions such as anxiety and panic disorders.[1] First-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) have been in clinical use for almost 60 years and have improved the quality of life for many people suffering from these illnesses.[2] But the benefits of these older antidepressants have been tempered by a range of adverse effects,[2] including QT interval prolongation.[3] Lengthening of the QT interval by these drugs may provoke torsades de pointes (TdP) and fatal ventricular arrhythmias.[4,5] However, these arrhythmias and TdP are quite rare. Most individuals with an abnormal QT do not experience these adverse events.[6,7] Second-generation antidepressants (selective serotonin reuptake inhibitors [SSRIs]) have now largely replaced first-generation antidepressants. These newer antidepressants appear to have a more favorable cardiovascular safety profile.[8,9] However, with an increasing number of patients receiving SSRIs, side effects that occur infrequently may become more apparent. In the last 2 decades, numerous case reports on cardiovascular side effects in users of SSRIs have appeared, including QT interval prolongation.[10,11] In 2011, the US Food and Drug Administration (FDA) issued a safety announcement[12] about the risks of QT prolongation and TdP by citalopram. Consequently, the drug labeling for citalopram was changed, recommending lower doses, especially in elderly patients.[13]

The possible association between therapeutic use of SSRIs and QT interval prolongation was studied in a limited number of controlled studies.[14–18] Despite the limited evidence, several SSRIs are now listed as QT-prolonging agents carrying a potential risk of TdP.[19] Furthermore, there is limited evidence as to whether the risk of QT interval prolongation is a property of specific SSRI agents or a class effect, ie, related to the common serotonin reuptake inhibiting mechanism of SSRIs. A previous study that investigated the association between use of SSRIs (as a class) and the occurrence of QT interval prolongation showed no overall increase in the QT interval duration in patients treated with SSRIs.[20] The aim of our study was to investigate the association between the use of SSRIs and the occurrence of QT interval prolongation in an elderly population.

METHOD

Setting and Study Design

This retrospective cross-sectional study was conducted at the University Medical Center Utrecht, the Netherlands. The study protocol was approved by the local hospital ethics board. Because the study only used routinely documented patient data, the ethics board waived the need for written informed consent. Patients over 60 years of age, who underwent outpatient preanesthesia evaluation in the period March 1, 2007, until March 1, 2012, were eligible to enter the study. Patients were identified by means of the hospital database containing information on preanesthesia evaluations. By hospital protocol, an electrocardiogram (ECG) is made routinely in all

Clinical Points

- Use of a selective serotonin reuptake inhibitor (SSRI) was not associated with the occurrence of QT interval prolongation in elderly surgical patients.
- The findings of our study do not justify avoidance of prescribing SSRIs in elderly patients.
- Clinicians should, however, be cautious when prescribing those SSRIs that are particularly suspected of QT prolongation, such as citalopram, and when treating a patient who is at high risk of developing cardiac arrhythmias due to certain comorbidities, such as heart failure, diabetes, or a history of myocardial infarction.

patients older than 60 years as part of the preanesthesia evaluation. Patients were excluded if they were scheduled for cardiac surgery, including electrocardioversion; if they had a pacemaker or previously had a cardiac transplantation; if their ECG showed premature ventricular contractions (as the measurement of QT is not reliable in case of premature ventricular contractions); if they used several antidepressants simultaneously; or if their medical record or ECG was missing.

Determinants

For this study, we included users of an SSRI and a matched sample of nonusers. The index group included patients reporting the use of an SSRI on the date of the outpatient preanesthesia evaluation. Selective serotonin reuptake inhibitors were classified according to the Anatomic Therapeutic Chemical system of the World Health organization.[21] The group of SSRIs included citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, and venlafaxine (maximum dose of 150 mg a day). If a patient visited the outpatient preanesthesia evaluation clinic more than once during the study period, we only included data from the first visit to avoid selection bias. If there was no ECG available at the first visit, the user of an SSRI was excluded, even if there was an ECG available at a possible second visit. The ECG had to be performed in a 3-week period before or after the preanesthesia evaluation, and in any case before surgery.

The reference group of nonusers of any antidepressant was matched to the index group on sex and year of scheduled surgery, but was otherwise randomly sampled from the study population in a 1-to-1 ratio with the index group. If a reference patient met the exclusion criteria, another suitable patient was randomly selected. Data on use of antidepressants were obtained from the electronic preanesthesia evaluation records.

Outcomes

The primary outcome was the occurrence of QT interval prolongation. As QT time is heart rate dependent, the QT interval corrected for heart rate (QTc) according to Bazett's formula was used: $QTc = QT/\sqrt{RR}$.[22] A prolonged QTc interval was defined as >450 milliseconds for males and >470 milliseconds for females.[23] A secondary outcome was the duration of the QTc interval.

A standard resting 12-lead ECG was recorded for preanesthesia evaluation (GE Healthcare, Eindhoven, the Netherlands). All ECGs were analyzed by using currently available software (GE MUSE software, GE Healthcare, Eindhoven, the Netherlands). The following characteristics were determined: heart rate (beats per minute [bpm]) and QT interval and QTc interval (milliseconds). Additionally, ECGs were visually evaluated by a physician (M.J.W.), experienced in ECG interpretation and blinded to group assignment, on the occurrence of atrial fibrillation and premature ventricular contractions.

Potential Confounders

The electronic preanesthesia evaluation records were assessed for potential confounding variables. Confounders assessed were patient characteristics and comorbidity, that is, weight and height, smoking, alcohol abuse, American Society of Anesthesiologists (ASA) preoperative physical status classification (a 5-point rating scale ranging from ASA 1 [healthy patient] to 5 [moribund patient not expected to survive without surgery]),[24] atrial fibrillation, diabetes mellitus, heart failure, hypertension, myocardial infarction, and pulmonary disease. The presence of diabetes mellitus, hypertension, and pulmonary diseases was assessed based on the patient's medication. In addition, comedications were assessed, that is, drugs listed as QT-prolonging agents with a proven risk or a possible risk of TdP (Table 1),[19] QT-shortening drugs (digoxin), and antiarrhythmic drugs.

Positive Control

To investigate whether our study population was suitable for detecting a QT-prolonging effect of drugs, we evaluated the effect of drugs listed as QT-prolonging agents with a known risk for TdP (Table 1).[19] Patients using this type of drugs were compared to patients not using these drugs on primary and secondary outcomes.

Data Analysis

Patient characteristics were described as numbers with percentages for nominal or ordinal data and means with standard deviations for continuous data. Comparison of the index and reference groups was performed by using the χ^2 test or Fisher exact test (where appropriate) for nominal data. Student independent sample *t* tests were used for comparison of continuous data when the data satisfied assumptions for parametric analysis. The Mann-Whitney *U* test was used for ordinal data or when continuous data did not satisfy assumptions for parametric analysis.

Conditional logistic regression analysis and linear regression analysis were used to estimate the strength of the association between the use of an SSRI and the occurrence of QTc prolongation and the duration of the QTc interval, respectively. To adjust for confounding effects, we calculated the individual probabilities for

Table 1. QT Prolonging Agents With a (known) Risk or Possible Risk of Torsades de Pointes[a]

Drugs With a (known) Risk	Drugs With a Possible Risk
Amiodarone	Alfuzosin
Arsenic trioxide	Amantadine
Astemizole	Artenimol + piperaquine
Azithromycin	Atazanavir
Bepridil	Chloral hydrate
Chloroquine	Clozapine
Chlorpromazine	Dolasetron
Cisapride	Dronedarone
Citalopram	Eribulin
Clarithromycin	Escitalopram
Disopyramide	Famotidine
Dofetilide	Felbamate
Domperidone	Fingolimod
Droperidol	Foscarnet
Erythromycin	Fosphenytoin
Flecainide	Gatifloxacin
Halofantrine	Gemifloxacin
Haloperidol	Granisetron
Ibutilide	Iloperidone
Levomethadyl	Indapamide
Mesoridazine	Isradipine
Methadone	Lapatinib
Moxifloxacin	Levofloxacin
Pentamidine	Lithium
Probucol	Moexipril/hydrochlorothiazide
Procainamide	Nicardipine
Quinidine	Nilotinib
Sevoflurane	Octreotide
Sotalol	Ofloxacin
Sparfloxacin	Ondansetron
Terfenadine	Oxytocin
Thioridazine	Paliperidone
Vandetanib	Perflutren lipid microspheres
	Quetiapine
	Ranolazine
	Risperidone
	Roxithromycin
	Sertindole
	Sunitinib
	Tacrolimus
	Tamoxifen
	Telithromycin
	Tizanidine
	Vardenafil
	Venlafaxine
	Voriconazole
	Ziprasidone

[a]Based on www.azcert.org.[19]

use of an SSRI (propensity score) and included them as a confounding factor in multivariable models. The propensity score for use of an SSRI was derived from a multivariable logistic regression model, including all variables that were significantly ($P < .1$) related to the use of an SSRI in univariate analysis.

We analyzed the effect of drugs listed as QT-prolonging agents with a known risk of TdP using logistic and linear regression analysis.

The strength of the association between the use of an SSRI and the occurrence of QTc interval prolongation was expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Differences in QTc time with 95% CIs were used to express the association between SSRI use and (actual) QTc interval duration.

Table 2. Characteristics of Selective Serotonin Reuptake Inhibitor Users and Reference Patients at Preoperative Evaluation

Characteristic	Index Group (n = 397)	Reference Group (n = 397)	*P* Value
Age, mean (SD), y	70 (7)	70 (7)	.30[a]
Body mass index (kg/m^2), mean (SD)	27 (5)	26 (4)	.11[a]
ASA classification, n (%)			
I	31 (8)	77 (19)	.00[b]
II	271 (68)	256 (65)	
III or more	95 (24)	64 (16)	
Smoking, n (%)	100 (25)	71 (18)	.01[c]
Alcohol abuse, n (%)	10 (3)	0 (0)	< .01[c]
Heart rate (ECG), mean (SD), bpm	70 (13)	72 (14)	.05[a]
Systolic blood pressure, mean (SD), mm Hg	141 (20)	144 (20)	.03[a]
Diastolic blood pressure, mean (SD), mm Hg	80 (11)	81 (11)	.33[a]
Comorbidity			
Atrial fibrillation (observed on ECG), n (%)	11 (3)	7 (2)	.34[c]
Hypertension, n (%)	216 (54)	194 (49)	.12[c]
Diabetes mellitus, n (%)	64 (16)	49 (12)	.13[c]
Pulmonary disease, n (%)	62 (16)	41 (10)	.03[c]
Heart failure, n (%)	5 (1)	1 (0.3)	.22[d]
History of myocardial infarction, n (%)	21 (5)	13 (3)	.16[c]
Comedication			
QT prolonging noncardiac medication with a risk of TdP, n (%)	29 (7)	18 (5)	.10[c]
QT prolonging noncardiac medication with a possible risk of TdP, n (%)	19 (5)	6 (2)	.01[c]
Antiarrhythmic medication, n (%)	26 (7)	22 (6)	.55[c]
Digoxin, n (%)	16 (4)	4 (1)	.01[c]

[a]Student independent sample *t* test. [b]Mann-Whitney *U* test. [c]χ^2 test. [d]Fisher exact test.
Abbreviations: ASA = American Society of Anesthesiologists, ECG = electrocardiogram, TdP = torsades de pointes.

RESULTS

During the study period, a total of 16,539 outpatient preanesthesia evaluations were performed among patients eligible for the study. Use of an SSRI was documented in 746 (4.5%) of these evaluations. Of these patients, 349 (47%) were excluded for the following reasons: concomitant use of multiple antidepressants (n = 90), not being a patient's first visit to the preanesthesia evaluation clinic (n = 168), lack of an ECG performed in a 3-week period before or after the preanesthesia evaluation (n = 57), an ECG showing premature ventricular contractions (n = 25), presence of a pacemaker (n = 8), or having undergone cardiac transplantation (n = 1). The remaining evaluations resulted in 397 unique index patients (53%).

In the index group of 397 patients, 114 patients (29%) used citalopram, 10 (3%) used escitalopram, 19 (5%) used fluoxetine, 22 (6%) used fluvoxamine, 172 (43%) used paroxetine, 16 (4%) used sertraline, and 44 (11%) used venlafaxine. In both the index and reference group, 154 patients (39%) were male. Table 2 summarizes general characteristics and comorbidity of the study patients. The

Table 3. QTc Interval Prolongation in SSRI Users Compared to Nonusers of Antidepressants

Variable	Index, n	Reference, n	QTc Interval[a] Prolonged,[b] n (%) Index Group (n = 397)	Reference Group (n = 397)	Crude Odds Ratios (95% CI)	Adjusted[c] Odds Ratios (95% CI)
Total	397	397	25 (6)	19 (5)	1.3 (0.7 to 2.4)	1.1 (0.5 to 2.0)
Citalopram	114	114	11 (10)	8 (7)	1.4 (0.6 to 3.4)	1.1 (0.4 to 2.9)
Escitalopram	10	10	0 (0)	0 (0)	…	…
Fluoxetine	19	19	1 (5)	1 (5)	1.0 (0.1 to 16)	…
Fluvoxamine	22	22	1 (5)	0 (0)	…	…
Sertraline	16	16	1 (6)	3 (19)	0.3 (0.0 to 3.2)	…
Paroxetine	172	172	10 (6)	5 (3)	2.0 (0.7 to 5.9)	1.5 (0.4 to 5.1)
Venlafaxine	44	44	1 (2)	2 (5)	0.5 (0.0 to 5.5)	

[a]According to Bazett's formula (QTc = QT/√RR).
[b]QTc interval > 450 milliseconds for males and > 470 milliseconds for females.
[c]Adjusted for propensity score on SSRI use.
Abbreviations: QTc = QT interval corrected for heart rate, SSRI = selective serotonin reuptake inhibitor.

Table 4. QTc Interval Duration in SSRI Users and Nonusers of Antidepressants

Variable	Index, n	Reference, n	QTc Interval[a] Duration, Mean (SD), ms Index Group (n = 397)	Reference Group (n = 397)	Crude ΔQTc (95% CI), ms	Adjusted[b] ΔQTc (95% CI), ms
Total	397	397	421 (23)	418 (22)	2.6 (−0.6 to 5.9)	1.5 (−1.8 to 4.8)
Citalopram	114	114	425 (27)	419 (23)	5.9 (−0.7 to 12.5)	5.4 (−1.6 to 12.3)
Escitalopram	10	10	416 (13)	424 (16)	−8.7 (−22.4 to 5.0)	…
Fluoxetine	19	19	423 (44)	419 (17)	4.4 (−17.3 to 26.1)	…
Fluvoxamine	22	22	413 (23)	415 (17)	−2.5 (−14.8 to 9.8)	…
Paroxetine	172	172	420 (22)	417 (20)	3.0 (−1.5 to 7.5)	1.6 (−2.9 to 6.1)
Sertraline	16	16	423 (23)	420 (23)	3.6 (−13.0 to 20.2)	…
Venlafaxine	44	44	417 (18)	420 (28)	3.5 (−13.4 to 6.3)	…

[a]According to Bazett's formula (QTc = QT/√RR).
[b]Adjusted for propensity score on SSRI use.
Abbreviations: QTc = QT interval corrected for heart rate, SSRI = selective serotonin reuptake inhibitor.

mean (SD) age of SSRI users and reference patients was 70 (7) years.

QTc interval prolongation occurred in 25 (6%) and 19 (5%) SSRI users and reference patients, respectively (Table 3). The propensity score predicting the probability of a patient using an SSRI was calculated. Factors significantly related to use of an SSRI were smoking, ASA classification, alcohol abuse, and pulmonary diseases. The area under the receiver operating characteristic curve of the propensity score was 0.67 (95% CI, 0.59 to 0.75). After adjustment for confounding factors by including the propensity score for use of an SSRI, users of an SSRI did not have a higher risk for QTc interval prolongation compared to nonusers (OR = 1.1; 95% CI, 0.5 to 2.0). There were no significant differences in the risk of QTc prolongation between users of the most frequently used SSRIs citalopram and paroxetine and their corresponding reference patients (Table 3).

Mean QTc interval length was not significantly higher in users of an SSRI compared with nonusers (difference of 2.6 milliseconds [95% CI, −0.6 to 5.9]). Adjustment for confounding factors revealed a difference of 1.5 milliseconds (95% CI, −1.8 to 4.8). There were no significant differences in mean QTc interval duration in users of citalopram and paroxetine and their corresponding reference patients (Table 4).

Forty-seven study patients used a drug listed as a QTc-prolonging agent with a known risk of TdP. Users of these drugs did have a higher risk for a prolonged QTc interval compared to nonusers (OR = 5.7; 95% CI, 2.6 to 12.3). In addition, the mean QTc interval duration was significantly higher in users of these QTc-prolonging agents compared with nonusers of such medication: a difference of 18.9 milliseconds (95% CI, 12.1 to 25.6).

DISCUSSION

This retrospective, cross-sectional study showed no significant association between the use of an SSRI and the occurrence of QT interval prolongation in a population of elderly surgical patients. The prolonging effect on the QT interval duration of 1.5 milliseconds in users of an SSRI compared to nonusers is not regarded to be clinically relevant.

Our results confirm the findings from the study by van Noord et al,[20] who did not find an increase in QT interval in SSRI users compared to nonusers. Nevertheless, certain SSRIs are currently listed as QT-prolonging agents with a known risk (citalopram), a possible risk (escitalopram), or a conditional risk (fluoxetine, paroxetine, and sertraline) of TdP.[19] In our study, the use of the most frequently used SSRIs, citalopram and paroxetine, was not associated with the occurrence of QT interval prolongation. In a recent epidemiologic study,[25] however, a small dose-dependent increase in QT interval was identified in a large group of citalopram users. We found a comparable small, but statistically not significant, difference

in QTc interval duration in users of citalopram compared with nonusers. This might be caused by the relative small sample size.

In recent years, several lists have been published of noncardiac drugs associated with QT prolongation and cardiac arrhythmias.[19,26,27] However, these lists are not identical and are mostly based on empirical data and incomplete evidence. Furthermore, if a drug of a similar therapeutic or chemical class is not on these lists, it is often unknown whether the drug actually does not provoke QT prolongation or whether it has been omitted due to a lack of data. Nevertheless, although this information on QT-prolonging agents does not seem completely reliable, it definitely influences clinicians in their decision to prescribe certain antidepressants in daily practice.

There is still discussion on defining the threshold for clinical significance of a drug-induced change in QT duration.[28] According to recent guidelines, new drugs receive an electrocardiographic evaluation to predict whether a new drug caries an increased risk of serious cardiac arrhythmias by QT interval prolongation. The objective of such an evaluation, known as a "thorough QT/QTc study," is to exclude that a new drug prolongs the QTc interval by 10 milliseconds or more. In addition, a positive control drug is included to demonstrate the study's ability to detect a small effect on the QTc interval of about 5 milliseconds.[29] A retrospective power analysis showed that our study was able to detect a difference of 4.6 milliseconds between users of an SSRI and nonusers. In the case of the citalopram and paroxetine subgroups, this difference was 8.6 milliseconds and 7.0 milliseconds, respectively. Therefore, a clinically relevant difference of 10 milliseconds, if present, could have been detected for both the total group of SSRI users and users of the individual SSRIs citalopram and paroxetine. Furthermore, we demonstrated a substantial QT interval prolonging effect of drugs listed as QT prolonging-agents with a known risk for TdP. This finding shows that our study population was suitable for measuring this outcome.

In a thorough QT/QTc study of citalopram, a mean change in QTc interval of 8.5 milliseconds was found for 20 mg per day and 18.5 milliseconds for 60 mg per day. On the basis of these findings, the FDA stated that citalopram should no longer be prescribed at doses of greater than 40 mg per day and that the maximum citalopram dose is 20 mg per day in elderly patients.[12] However, there is still no consensus whether an increase in QTc of this magnitude (< 20 milliseconds) for a dosage of 60 mg is clinically relevant.[4,28] The guidelines of the Committee for Proprietary Medicinal Products (CMPC) suggest that individual changes of QTc interval length need to be at least between 30 and 60 milliseconds from baseline to raise concern for potential risk of drug-induced arrhythmias.[23] Another commonly accepted threshold for a clinically significant drug-induced change in QTc length is even higher, with an increase ≥ 60 milliseconds.[28,30] On the other hand, some QTc-prolonging drugs that were withdrawn from the market because of TdP were associated with a QTc interval prolongation of only 5 to 10 milliseconds in certain patient populations.[31] We found a small increase in QTc duration of about 2 milliseconds in the total group of SSRI users compared to nonusers, which was not statistically significant. The mean increase in QTc interval in users of citalopram was approximately 5 milliseconds compared to nonusers. According to the changed drug's label in Europe and the United States, the maximum recommended dose of citalopram is currently 20 mg per day for patients older than 60 and 65 years of age, respectively. In our study, 23 of the 114 citalopram users (> 60 years) were treated with a dose greater than 20 mg per day. In 3 of them, QTc prolongation occurred, and, in 1 patient, the QTc interval was > 500 milliseconds. However, the evidence for dose-dependent effects of citalopram on QT prolongation is not only limited but also conflicting.[12,20,25,32]

The definition for clinically relevant QTc prolongation also differs in the literature. We used the cutoff points for a prolonged QTc interval according to CMPC guidelines.[23] Another suggested threshold is a QTc interval ≥ 500 milliseconds.[4,28,30,33] In our study, 5 users of an SSRI and no reference patients showed a QTc interval ≥ 500 milliseconds. However, although the QTc interval is considered the most valid surrogate marker for TdP, the association is not entirely clear. A QTc interval below a certain value is not a guarantee that patients will not develop TdP, particularly in the context of other factors that may provoke cardiac arrhythmias, such as electrolyte disturbances or heart failure.[4]

The possible mechanism underlying SSRI-induced QT prolongation is not completely clear. Both sodium channels and human ether-a-go-go (hERG) potassium channels may be involved. Blocking cardiac potassium channels results in prolongation of the myocyte action potential. This appears as an increase in the duration of the QT interval on the ECG. Besides being a direct blockade of the hERG potassium channels, SSRIs may also disrupt the hERG protein expression on the cell membrane, resulting in a reduced number of hERG potassium channels.[34]

This study was conducted in a population of elderly surgical patients. We used retrospective data from outpatient preanesthesia evaluation during a 5-year period. In this way, we were able to include almost 400 different users of an SSRI and corresponding reference patients. All data on primary and secondary outcomes were obtained from the routinely made ECGs. Furthermore, we collected other factors that may have influenced outcomes, such as comorbidity and comedication, including drugs listed as QT-prolonging or -shortening agents. This allowed us to perform adjustments for confounding by including the propensity score for use of an SSRI in the analysis.

Still, some potential limitations of our study have to be addressed. First, this study was a retrospective, nonrandomized cross-sectional study and therefore was subject to potential bias. Due to the nature of the study, we were unable to identify those patients in whom the use of an SSRI was discontinued because of QT interval prolongation or, in the worst case, was fatal. Therefore, the effect of SSRI use on the QT interval might have been underestimated. To

minimize further selection bias, we selected all users of an SSRI and reference patients from a well-defined population of elderly surgical patients without knowledge of outcome parameters at the time of selection. Furthermore, to avoid inclusion of the same patient more than once, only a patient's first visit to the outpatient preanesthesia evaluation clinic in the study period was included. Second, the number of users of certain individual SSRIs was quite small. This limited further conclusions for these SSRIs. Third, our study population consisted of a defined group of elderly surgical patients. Further investigation is needed to assess the effect of SSRIs on QT prolongation in other patient populations. Fourth, the FDA announcement in August 2011 may have influenced SSRI prescribing. However, in our study, 93% of the study patients were included before the FDA warning. A separate analysis of the data of these patients did not alter the results. Fifth, we used Bazett's formula to correct the QT for heart rate. This formula may tend to undercorrect for lower heart rates and overcorrect for higher heart rates. However, this formula is (most) frequently used in QT studies and was a standardized correction in the ECG software. Sixth, possible susceptibility of individual patients to SSRI-induced QT interval prolongations resulting from hERG polymorphism was not accounted for in this study.

In summary, use of an SSRI was not associated with the occurrence of QT interval prolongation in elderly surgical patients. On the basis of our findings, it seems reasonable not to advocate avoidance of prescription of these antidepressants in the elderly. However, prescribers of SSRIs should be aware of the potential risk of QT interval prolongation, especially when prescribing those SSRIs that are particularly suspected for QT prolongation with the attendant risk of TdP, such as citalopram. Furthermore, one should be cautious when a patient is at higher risk of developing cardiac arrhythmias by having certain comorbidities, such as heart failure, diabetes, or a history of myocardial infarction.[4,20] If there is still doubt about the risks and benefits of the use of an SSRI in an individual patient, consultation between the psychiatrist or general practitioner and the cardiologist is indicated before starting an SSRI. If necessary, special precautions should be taken, such as routine control of ECG.

Drug names: citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), digoxin (Lanoxin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), iloperidone (Fanapt), lithium (Lithobid and others), methadone (Methadose and others), ondansetron (Zofran and others), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), vardenafil (Levitra and others), venlafaxine (Effexor and others), ziprasidone (Geodon and others).

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