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Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: a review of the evidence

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Abstract: Antidepressants are widely used medications for a range of medical conditions such as mood disorders and chronic pain in older adults. A vast body of evidence exists concerning the risks of QT interval prolongation associated with these agents and healthcare providers should critically evaluate the potential for QT prolongation when selecting antidepressant agents. Long QT syndrome is a disorder of myocardial repolarization that manifests as a prolonged QT interval on an electrocardiogram (ECG) and has been demonstrated to increase with age. The objective of this review is to present and evaluate existing literature regarding the risk of QT prolongation in older adults, age 60 years and older, and discuss the implications for clinical practice. A PubMed search was conducted to identify studies evaluating the QT prolonging effects of antidepressant medications and publications were chosen based on pertinent criteria. Depending on the antidepressant agent and patient-specific factors, clinicians should assess and monitor electrolytes and EGCs to evaluate the risks and benefits for older adults receiving agents known to prolong the QT interval.

Keywords: antidepressants, antidepressive agents, elderly, long QT syndrome, long QT syndrome/chemically induced, older adults, QT prolongation, QTc interval

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Introduction

The QT interval, most often reported as the corrected (for heart rate) QT interval or QTc, is an electrocardiographic measure of ventricular repolarization and depolarization.[1] A normal QT interval is less than 450 ms in men and 460 ms in women.[2] A number of drugs have been implicated in prolongation of the QT interval, including antiarrhythmics, antipsychotics, certain antibiotics, and a number of antidepressants.[3] Risk factors for QT prolongation include female sex, age greater than 65 years, electrolyte disturbances (hypokalemia, hypomagnesemia), concomitant QT prolonging medications, and a number of disease states (hypertension, diabetes, stroke).[4]

Several formulas have been developed to analyze the QTc interval that correct for heart rate. Two of the formulas are Bazett's and Fridericia's, which are mentioned later in this review. A common threshold used to define a QT interval at high risk for arrhythmia is 500 ms.[5] Torsades de Pointes (TdP) is an uncommon, but potentially lethal polymorphic ventricular tachycardia associated with a prolonged QTc interval.[6] The United States Food and Drug Administration (FDA) ICH E14 Guidance for Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs established the thresholds seen in Table 1.[7]

The trend of increasing risk for QTc prolongation with aging makes assessing the risk of drug-induced QTc prolongation in older adults an intriguing area of research. Antidepressant agents are a commonly implicated class of medications in prolongation of the QTc interval,[3] and the prevalence of older adults on antidepressant therapy is on the rise, with 19.1% of adults over 60 years of age in the United States using antidepressants from 2011 to 2014.[8] While the American Geriatrics Society (AGS) 2015 Updated Beers

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Table 1. US FDA E14 guidance for drug-induced QTc prolongation.

Change from baseline QTc placebo correct	Interpretation
<10 ms	Low concern
10–20 ms, +QTc outliers, ± clinical AEs	Increasing concern
>20 ms, +QTc outliers, ± clinical AEs	Definite concern

QTc outliers: individual-level QTc > 500 ms or change in QTc > 60 ms.
Clinical AEs: TdP, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, syncope, seizure.
AE, adverse event; TdP, Torsades de Pointes; US FDA, US Food and Drug Administration.

Criteria recommends avoiding certain antidepressants, including a number of tricyclic agents and paroxetine, these recommendations are based primarily on anticholinergic effects and not potential cardiovascular risk.[9] QTc prolongation is more common in older patients with severe mental illness, as evidenced by data from Veteran's Health Administration patients from October 2005 to September 2009; however, it is important to note this may be confounded by medical conditions or medications.[10] While several review articles exist investigating the QT prolonging effects of antidepressants, the older adult patient population has not been specifically addressed in detail in these reviews. The increased prevalence of antidepressant use in the US, particularly among older adults, warrants specific investigation. In this review, we discuss the QTc prolonging effects of antidepressants in older adults.

Methods

A *PubMed* search was conducted in December 2017 to identify studies found through 2017 evaluating the QTc prolonging effects of antidepressants in older adults. The following MeSH terms were used: antidepressive agents AND the following terms (separately): aged, long QT syndrome/chemically induced. Additionally, the following search terms were added to the search with OR: Antidepressant Drugs, Antidepressants, Thymoanaleptics, Thymoleptics, Sertraline, Zoloft, Paroxetine, Paxil, Citalopram, Celexa, Escitalopram, Lexapro, Fluoxetine, Prozac, Fluvoxamine, Luvox, Desvenlafaxine, Pristiq, Duloxetine, Cymbalta, Levomilnacipran, Fetzima, Milnacipran, Savella, Venlafaxine, Effexor, Vilazodone, Viibryd, Vortioxetine, Trintellix, Nefazodone, Serzone, Trazodone, Desyrel, Bupropion, Wellbutrin, Amitriptyline, Elavil, Clomipramine, Anafranil, Desipramine, Norpramin, Doxepin, Sinequan, Nortriptyline, Pamelor, Mirtazapine, Remeron, elderly, and QTc interval or QTc prolongation. All searches were combined to comprise the full literature search. Bibliographies were also reviewed for inclusion of additional studies. Case-control studies, prospective and retrospective cohort studies, cohort, randomized controlled trials, and case reports were included. Studies including primarily adults under 60 years, drugs other than antidepressants, and not including QTc interval were excluded. In addition, studies not published in English and not conducted in humans were excluded. Study titles and abstracts were reviewed and publications were selected based on the following criteria: study population primarily over 60 years of age, mean age over 60 years, or significant proportion (>25%) of study population under 60 years of age, in addition to evaluating changes in the QTc interval. Studies that evaluated combination therapy with antipsychotics and antidepressants were excluded as the primary focus of this review is to evaluate the QTc prolonging effects of antidepressant therapy while minimizing confounders. The threshold age of 60 years was selected in lieu of the Medicare defined threshold of 65 years because a number of studies implemented an age threshold for older adults of 60 years or greater. A small number of studies with a mean age less than 60 years were also included due to significant proportions of study populations meeting the threshold of 60 years or greater. A summary of search results and study selection can be found in Figure 1.

Results

Tricyclic antidepressants

The tricyclic antidepressants (TCAs) are included in the 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults based primarily on their anticholinergic properties leading to poor safety profiles.[9] The impact of these agents on the QTc interval is well documented.[11–19] The effects of specific agents will be discussed below, and a summary of effects on the QTc interval can be found in Table 2.

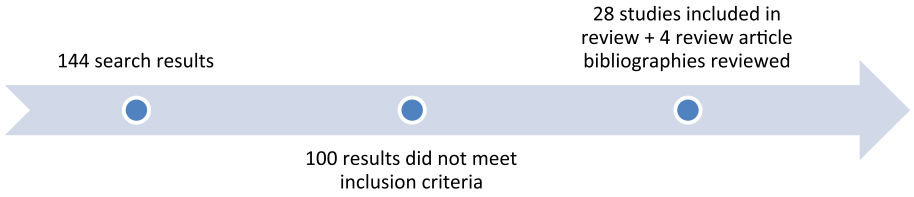

Figure 1. Summary of search results and study inclusion.

A subset of the Rotterdam study, a prospective, population-based cohort study, investigated the QTc prolonging effects of TCAs.[11] The drugs investigated in the study included amitriptyline, maprolitine, clomipramine, imipramine, nortriptyline, doxepin, and dosulepin. The authors reported cross-sectional and longitudinal analyses comparing electrocardiograms (ECGs) made during TCA use with those made during nonuse. Changes in QTc using the Bazett and Fridericia formula were reported as well as correction using linear regression coefficients. The cross-sectional analysis demonstrated statistically significant QTc prolongation with amitriptyline, maprolitine, imipramine, and nortriptyline using Bazett corrected QTc interval, with an average of 6.5 ms [95% confidence interval (CI) 4.0–9.0]. TCA use was associated with an overall increase in heart rate of 5.8 beats per minute. Furthermore, when adjusted for heart rate, the statistical significance observed with increased QTc using the Bazett formula was lost.

Tricyclic antidepressants are also used as adjuvant therapy in the treatment of neuropathic pain. A single-center, retrospective, observational study conducted by Funai and colleagues at Osaka City University Hospital in Japan evaluated 87 patients (65 on amitriptyline and 22 on nortriptyline) receiving TCAs for herpes zoster pain or postherpetic neuralgia.[12] Median daily doses were 25 mg daily for amitriptyline and 10 mg daily for nortriptyline, which are lower than normal doses used in the treatment of depression. The authors found that TCAs significantly prolonged the QTc interval from 413.2 ± 17 ms before treatment to 419.9 ± 18.9 ms, $p < 0.01$.

A longitudinal, prospective study by da Cunha and colleagues involving low-dose TCA therapy in the treatment of chronic pain investigated the effects of amitriptyline and imipramine on the QTc interval among other measures of cardiac conduction.[13] The study found no significant impact of a mean dose of 54.29 mg of amitriptyline and 46.87 mg of imipramine on QTc interval at 30 and 60 days of therapy.

A self-controlled crossover study conducted by Iribarren and colleagues investigated the effects of drugs known to impact the QT interval.[14] The mean age of the study cohort was 56 years; however, the study included 17,669 patients aged 65 years and older (29.7% of the cohort). The authors reported a change in the log-linear regression corrected QT interval, QT_{creg}, as well as correction with the Bazett formula. Trimipramine, clomipramine, doxepin, imipramine, amitriptyline, desipramine, and nortriptyline all affected a mean increase in the QTc interval between 10 and 20 ms, while protriptyline's mean increase of 9.5 ms failed to reach significance.

An extension of the Rotterdam study investigated the QTc prolonging effects of psychotropic medications across four follow-up visits spanning the years 1990–2005.[15] ECGs of patients using cardiovascular drugs listed as QTc prolonging agents were excluded. As a class, the TCAs resulted in a 6.9 ms increase in the QTc interval (95% CI 3.1–10.7), with nortriptyline having the greatest increase in QTc at 23.3 ms (95% CI 7.7–38.9 ms); however, there were only six subjects in the trial.

McCue and colleagues investigated the electrocardiographic effects of nortriptyline in 31 elderly patients receiving treatment for depression.[16] The mean daily dose of nortriptyline was 83.9 mg [standard deviation (SD) 24.4 mg]. The study found that the mean baseline QTc interval was measured at 400 ms (SD 30 ms) and increased to 430 ms (SD 30 ms, $p < 0.001$) at week 7.

Spindelegger and colleagues completed a drug surveillance report detailing cardiovascular adverse reactions (ADRs) in German-speaking countries from 1993 to 2010.[17] There were 198 cardiovascular ADRs observed, including 19 cases of QTc prolongation. All but one case of

Table 2. Selected QTc interval changes reported by study.

Drugs investigated	Number of patients	Mean age of patients in study (SD)	Change in QTc interval, ms	Reference
Tricyclic antidepressants (TCAs)				
Amitriptyline	65	70.3 (±7.5)	7.1, SD (±13.8)	Funai and colleagues[12]
Nortriptyline	22		5.6, SD (±21.8)	
Amitriptyline	40 (total for both drugs)	57.27 (±13.65)	No significant change	da Cunha and colleagues[13]
Imipramine				
Trimipramine	14	56 (±17)	18.6 (95% CI 2.7–34.4)	Iribarren and colleagues[14]
Clomipramine	53		18.4 (95% CI 11.5–25.3)	
Doxepin	538		12.8 (95% CI 10.4–15.2)	
Imipramine	998		11.8 (95% CI 10.1–13.5)	
Amitriptyline	2655		11.6 (95% CI 10.5–12.6)	
Desipramine	289		11.4 (95% CI 8.2–14.5)	
Nortriptyline	2591		10.9 (95% CI 9.9–12.0)	
Any TCA	66	66.7 (±8.6)	10.4 (95% CI 3.5–17.4)	Van Noord and colleagues[15]
Amitriptyline	37		8.5 (95% CI 2.8–14.2)	
Clomipramine	11		6.0 (95% CI −4.9, 17.0)	
Doxepin	1		n/a	
Imipramine	1		n/a	
Maprotiline	12		13.9 (95% CI 3.6–24.3)	
Nortriptyline	4		35.3 (95% CI 8.0–62.6)	
Any TCA	331	65.1 (±9.8)	6.5 (95% CI 4.0–9.0)	Noordam and colleagues[11]
Amitriptyline	200		5.5 (95% CI 2.3–8.8)	
Maprotiline	56		10.8 (95% CI 4.9–16.7)	
Clomipramine	31		3.6 (95% CI −4.0, 11.1)	
Imipramine	17		11.3 (95% CI 0.7–21.9)	
Nortriptyline	16		13.0 (95% CI 1.8–24.2)	
Doxepin	7		−7.8 (95% CI −24.3, 22.8)	
Dosulepin	4		−2.2 (95% CI −27.2, 22.7)	
Selective serotonin reuptake inhibitors (SSRIs)				

Table 2. (Continued)

Drugs investigated	Number of patients	Mean age of patients in study (SD)	Change in QTc interval, ms	Reference
Fluoxetine	8537		13.0 (95% CI 12.4–13.6)	Iribarren and colleagues[14]
Paroxetine	4531		12.4 (95% CI 11.6–13.2)	
Sertraline	1834		11.6 (95% CI 10.3–12.9)	
Citalopram	2005		10.4 (95% CI 9.2–11.6)	
Any SSRI	82		13.9 (95% CI 3.6–24.3)	Van Noord and colleagues[15]
Citalopram	1		35.3 (95% CI 8.0–62.6)	
Fluoxetine	8		−2.4 (95% CI −10.1, 5.4)	
Fluvoxamine	54		n/a	
Paroxetine	9		−5.6 (95% CI −18.4, 7.2)	
Sertraline	5		−19.4 (95% CI −31.0, −7.8)	
Mianserin	1		2.6 (95% CI −2.1, 7.2)	
Cross-sectional analysis		65.2 (±9.8)		Maljuric and colleagues[20]
SSRIs	436		2.9 (90% CI 1.3–4.5)	
Fluoxetine	39		4.5 (90% CI −0.4–9.3)	
Citalopram	35		12.8 (90% CI 7.3–18.2)	
Paroxetine	263		1.7 (90% CI −0.4, 3.7)	
Sertraline	42		1.7 (90% CI −3.4, 6.9)	
Fluvoxamine	52		1.7 (90% CI −2.9, 6.3)	
Escitalopram	5		2.7 (90% CI −11.6, 16.9)	
Longitudinal analysis, exposure definition 1*				
SSRIs	189		1.6 (90% CI −0.3, 3.5)	
Fluoxetine	14		−5.9 (90% CI −12.9, 1.2)	
Citalopram	10		21.5 (90% CI 12.1–30.8)	
Paroxetine	120		2.2 (90% CI −0.1, 4.6)	
Sertraline	19		−4.4 (90% CI −10.4, 1.7)	
Fluvoxamine	24		0.1 (90% CI −5.2, 5.4)	
Longitudinal analysis, exposure definition 2$				
SSRIs	114		1.1 (90% CI −1.6, 3.8)	
Fluoxetine	11		−3.9 (90% CI −12.6, 4.9)	

(Continued)

Table 2. (Continued)

Drugs investigated	Number of patients	Mean age of patients in study (SD)	Change in QTc interval, ms	Reference
Citalopram	5		28.9 (90% CI 15.3–42.5)	
Paroxetine	69		1.9 (90% CI −1.7, 5.6)	
Sertraline	12		−5.8 (90% CI −14.5, 2.9)	
Fluvoxamine	12		−10.8 (90% CI −19.3, −2.3)	
Citalopram	22	78 (±8)	18.1 ((95% CI 6.1–30.1)	Drye and colleagues[21]
SSRIs	397	70 (±7)	2.6 (95% CI −0.6, 5.9)	van Haelst and colleagues[22]
Citalopram	114		5.9 (95% CI −0.7, 12.5)	
Escitalopram	10		−8.7 (95% CI −22.4, 5.0)	
Fluoxetine	19		4.4 (95% CI −17.3, 26.1)	
Fluvoxamine	22		−2.5 (95% CI −14.8, 9.8)	
Sertraline	16		3.6 (95% CI −13.0, 20.2)	
Paroxetine	172		3.0 (95% CI −1.5, 7.5)	
Nortriptyline	31	64.4	30 ms ($p < 0.001$)	McCue and colleagues[16]
Serotonin norepinephrine reuptake inhibitors				
Duloxetine 60 mg daily	311	72 (median)	Not significant	Raskin and colleagues[23]
Duloxetine 120 mg total daily dose	449	59.9 (±10.5)	Not significant	Raskin and colleagues[24]
Venlafaxine	1442		10.6 (95% CI 9.2–12.0)	Iribarren and colleagues[14]
Venlafaxine	44		3.5 (95% CI −13.4, 6.3)	Van Haelst and colleagues[22]
Other antidepressants				
Trazodone	12		−12.1 (95% CI −25.6, 1.4)	Van Noord and colleagues[15]

*Exposure definition 1: SSRI use at subsequent ECG irrespective of SSRI use at prior ECG.
$exposure definition 2: SSRI use at subsequent ECG with no SSRI use at prior ECG.
CI, confidence interval; ECG, electrocardiogram; n/a, insufficient data; SD, standard deviation.

QTc prolongation involved a QTc increase of over 500 ms, while one was an increase from 300 to 460 ms. No cases of statistically significant QTc prolongation were discovered with citalopram or escitalopram monotherapy (the cases identified involved patients on combination therapy with an antipsychotic, TCA, or anticonvulsant). TCAs accounted for more than half of the QTc prolongation events in the study. Overall, the incidence of QTc prolongation in this study

failed to demonstrate statistical significance for any antidepressant exposure. The lack of demonstrable QTc prolongation in this study was a direct result of the study's data source being limited to severe cardiovascular ADRs in hospitalized patients and therefore failed to capture less significant QTc interval changes that would be seen with routine outpatient monitoring. Nonetheless, this study demonstrates that among cases of QTc prolongation leading to hospitalization, TCAs are more commonly implicated than other antidepressant agents.

A review of hospitalizations for TCA overdose by Kresse-Hermsdorf and colleagues found the most common adverse effect of a TCA overdose was having a prolonged QT interval.[18]

Selective serotonin reuptake inhibitors

The cardiovascular safety profile of selective serotonin reuptake inhibitors (SSRIs) is a keen topic of research, as these agents are recommended as first-line therapy in the management of geriatric depression.[19] While these agents are generally selected due to their favorable safety profiles, the FDA announced a recommendation to restrict the maximum dose of citalopram in patients aged 60 years and older to 20 mg daily.[25] Available data for specific agents is discussed below, and a summary of effects on QTc interval can be found in Table 2.

The CitAD was a randomized, double-masked, placebo-controlled, multicenter clinical trial for agitation in Alzheimer's disease (AD). A total of 186 patients were assigned to citalopram (target dose of 30 mg/day) or placebo in a 1:1 ratio. Interestingly, the study spanned a period of time before and after the FDA's safety communication about restricting citalopram dosage to 20 mg daily in adults 60 years and older. After the citalopram safety communication, ECG monitoring was added to the required study procedures before enrollment and repeated at week 3 to monitor change in QTc interval. Forty-eight patients were enrolled after enhanced electrocardiographic monitoring began.[21] Twenty-two patients in the citalopram group completed an ECG at baseline and week 3. The mean change in QTc interval with citalopram was 18.1 ms (95% CI 6.1–30.1), including seven patients with a QTc interval that increased by at least 30 ms. Of note, one of 22 placebo patients also experienced an increase in QTc interval by 30 ms during an ECG.

Van Haelst and colleagues conducted a retrospective cross-sectional study investigating the association between SSRI use and QTc prolongation in an elderly surgical population.[22] Notably, patients on other QT prolonging drugs (including antiarrhythmics) were not excluded from the study, and significantly more patients in the SSRI group were on a QT prolonging noncardiac medication with a possible risk of TdP (19 *versus* 6 patients respectively, $p < 0.01$). QTc outcomes assessed included a prolonged QTc interval (>450 ms for men and >470 ms for women), and the mean change in QTc was adjusted for propensity score on SSRI use. SSRIs were not associated with a statistically significant increase in the incidence of QTc prolongation or a significantly prolonged QTc interval.

The Rotterdam study was a prospective study conducted from 1991 to 2012 in The Netherlands. Maljuric and colleagues conducted an arm of the study examining the effect of SSRIs on the Fridericia corrected QT interval (QTc_f) where 12,589 patients and 26,260 ECGs (436 of which were during SSRI use) were included.[20] The cross-sectional analysis of ECGs of 436 SSRI users demonstrated an overall QTc_f increase of 2.9 ms (90% CI 1.3–4.5). The only agent that caused an increase greater than 10 ms was citalopram, with a mean increase in QTc_f of 12.8 ms (90% CI 7.3–18.2) in 35 subjects. The longitudinal analysis of this trial demonstrated no statistically significant class effect while citalopram maintained a significant increase in QTc_f regardless of exposure definition (change in QTc_f regardless of SSRI use in subsequent visits, and change in QTc_f with no SSRI use at prior visit).

The Rotterdam extension study by van Noord and colleagues also included patients taking SSRIs.[15] In the total analysis of patients receiving SSRI therapy, the change in QTc interval failed to reach a statistically significant increase at 0.1 ms (95% CI −1.7, 1.8). The only SSRI that demonstrated any increase in the QTc interval was citalopram at 6.5 ms, but it failed to demonstrate statistical significance (95% CI −13.7, 26.7).

Iribarren and colleagues studied patients taking a number of SSRIs.[14] The following mean increases in QTc were fluoxetine, 13.0 ms (12.4–13.6), paroxetine, 12.4 ms (11.6–13.2), sertraline, 11.6 ms (10.3–12.9), and citalopram, 10.4 ms (9.2–11.6).

Furthermore, there have been case reports of TdP with citalopram and fluoxetine in women over the age of 80 years. In both cases, the QTc interval normalized upon discontinuation of the agents.[26,27]

Serotonin norepinephrine reuptake inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) are typically used as second-line agents in the management of geriatric depression, and can be used for management of neuropathic pain.

An 8-week multicenter, randomized, double-blind, placebo-controlled study of 311 elderly patients conducted by Raskin and colleagues investigated the safety and tolerability of duloxetine 60 mg daily in the treatment of major depressive disorder.[23] The change in the QTc interval compared with placebo was not significant when corrected by the Bazett and Fridericia method, QTcB (duloxetine, 1.63; placebo, 2.49; p = 0.706) and QTcF (duloxetine, 2.26; placebo, 1.60; p = 0.775).

A 28-week, open-label study conducted by Raskin and colleagues randomized patients with diabetic peripheral neuropathic pain (DPNP) in a 3:1 ratio to duloxetine 60 mg twice daily or 120 mg once daily.[24] ECGs were collected at baseline and weeks 7, 19, and 27 or early discontinuation. There was no significant increase in QT interval in either treatment group, while the 60 mg twice daily group demonstrated a significant decrease in QT corrected for heart rate (Fridericia): –2.33 ms ± 17.71 ms (p = 0.023).

A 12-week open-label study conducted by Johnson and colleagues investigated the cardiovascular effects of venlafaxine in the treatment of major depressive disorder in patients aged 60 years and older.[28] Sixty-two participants started the trial and 59 completed it. The mean maximum dose of venlafaxine prescribed was 209.5 mg/day, ranging from 75 to 300 mg daily. The QTc interval at baseline was 424.0 ms (SD 21.3) and 422.1 ms (SD 21.2) at week 12 (p = 0.81).

Iribarren and colleagues' study previously mentioned also included patients receiving SNRI therapy. Venlafaxine effected a mean increase in the QTc interval of 10.6 ms (95% CI 9.2–12.0).[14] Six patients on venlafaxine were included in the Rotterdam extension study.[15] Venlafaxine did not cause a statistically significant increase in the QTc interval, 6.3 ms (95% CI −9.5 to 22.2); however, there has been a case report of QTc prolongation with venlafaxine use.[29]

Other antidepressants

A number of non-SSRI antidepressants have been developed, but there is a paucity of evidence regarding their effects on the QT interval.

Bupropion

Bupropion is a monocyclic antidepressant that primarily functions as an inhibitor of dopamine and norepinephrine reuptake.[30] A single double-blind trial by Wenger and colleagues looked at the cardiac effects of bupropion and amitriptyline.[31] While the trial did not look specifically at elderly patients, it provides some insight into bupropion's cardiac effects. Bupropion resulted in a mean QTc reduction of 3.6 ms with a mean dose of 552 mg (maximum in study 750 mg), exceeding labelled dosing recommendations.

Mirtazapine

Mirtazapine was approved by the FDA in 1997. Its mechanism of antidepressant action is not well known, but it is thought to have serotonergic and noradrenergic properties.[32] The package insert advises caution when prescribing mirtazapine to elderly patients due to decreased clearance.[32]

Among 12 patients included in the Rotterdam extension study, mirtazapine resulted in a QTc increase of 8.1 ms, but failed to reach statistical significance (–4.2, 20.4).[15] Trazodone and mianserin also demonstrated no significant increase in QTc interval.

Mirtazipine was identified in a study by Danielsson and colleagues[33] as having a higher adjusted hazard ratio for all-cause mortality in elderly patients. Using the TdP risk levels established by CredibleMeds, the data indicating a higher adjusted hazard ratio for death may be due to the potential to alter the cardiac tissue's ability to repolarize.

Other agents

There are no published data regarding QTc prolongation outside of premarketing studies in the package insert for desvenlafaxine and levomilnacipran, likely due to both agents being new to their drug class.[34,35] Additionally, there are no

reports of a prolonged QTc interval in older adults taking vilazodone.

Discussion

The level of risk associated with QTc prolonging agents can be difficult to interpret, even in the context of FDA recommendations. A rare outcome associated with QTc prolonging agents is the risk of sudden death. A case-control study conducted by Jolly and colleagues matched 1010 patients who died suddenly, without a clear cause of death, with 3030 matched living controls from primary care.[36] The mean age of cases and controls was 67.6 years. The authors found SSRIs significantly increased the risk for sudden death, 2.21 (1.61, 3.05), and tricyclic antidepressants trended towards increased risk but failed to reach statistical significance, 1.44 (0.96, 2.13). These results remained consistent when the odds ratios were adjusted for heart failure, myocardial infarction, atrial fibrillation, revascularization, hypokalemia, bradycardia, syncope, epilepsy, renal dysfunction, and history of alcohol abuse. This study demonstrates that QTc prolonging risk is not a sole predictor of mortality when evaluating antidepressant therapy in older adults.

Furthermore, our study has several limitations. We did include case reports to include any report of QT prolongation, specifically in older adults. These case reports were more common in the recently approved antidepressants for which a risk of QT prolongation has been listed as a warning but not confirmed in a large study. By including case reports, bias is introduced and validity regarding conclusions with these specific medications is limited.

TCAs

The studies included in this review present a mixed picture of the QT prolonging effects of the TCAs. The results of the study by Noordam and colleagues[11] provide interesting insight into the methods used to correct the measured QT interval. The Bazett formula appears to overestimate the corrected QT interval in patients with an elevated heart rate. The authors noted a significant increase in heart rate with TCA therapy. The other methods of QT correction used in the study revealed no significant increase in QT interval. This suggests that while TCAs have a poor cardiovascular safety profile, the risk may be more attributable to heart rate elevation, heart failure, and overall increased risk of cardiovascular mortality.[37] The remainder of the studies of TCAs in patients treated for depression reflect an increase in QTc in the range of 10–20 ms, a cause for increasing concern according to the FDA's E14 criteria.[7] Funai and colleagues demonstrated that low-dose TCAs used in the treatment of neuropathic pain prolong the QT interval, but to a lesser degree than seen with antidepressant doses.[12] There is certainly sufficient evidence to show that TCAs significantly prolong the QT interval in the elderly, but their anticholinergic effects and unfavorable safety profiles provide stronger justification for avoiding their use in the geriatric population.

SSRIs, SNRIs, and other antidepressants

At a glance, the CredibleMeds database implicates SSRIs as a class in QTc prolongation.[3] Even in elderly patients, the only SSRI that causes consistently significant QTc prolongation is citalopram, which is consistent with FDA recommendations.[14,20,21] This is not to say that use of the other SSRIs is not without risk. Pharmacokinetic interactions and the addition of other QTc prolonging medications can greatly influence arrhythmic risk. Among the SNRIs, duloxetine has demonstrated a lack of effect on the QTc interval.[23,24] The results with venlafaxine were mixed, and the largest population of patients on venlafaxine experienced a mean change in QTc interval of 10.6 ms.[14] The other two trials involving venlafaxine did not reflect significant increases in the QTc interval.[15,22] Insufficient evidence exists in elderly patients regarding the QTc prolonging effects of other antidepressants such as bupropion, levomilnacipran, and vilazodone. While preliminary evidence in healthy subjects is promising, more studies are needed in elderly patients with comorbidities to elucidate the safety of the newer antidepressant agents. In the setting of neuropathic pain, or depression treatment failure with multiple SSRIs, it may be prudent to consider duloxetine in geriatric patients.

Patient considerations

The aim of this study was to summarize the current data with regards to QTc prolonging antidepressant agents in the elderly. It is also important to assess risk factors common in the elderly patient population. Danielsson and colleagues identified risk factors common to the elderly: heart disease, electrolyte changes, multiple QTc

prolonging agents used simultaneously, and comorbid conditions that reduce the ability to metabolize or excrete drugs that prolong the QT interval.[33] Furthermore, female sex is another risk factor to take into consideration, especially when initiating therapy of a QT prolonging medication. Studies have shown that women have a 10–20 ms longer QTc interval at baseline compared with men and have a higher risk for developing drug-induced TdP.[38] This increased risk is thought to be due to higher plasma concentrations of QT prolonging medications or having a greater sensitivity for QT prolonging effects.[38]

Additionally, cognitive dysfunction should be considered when identifying patients that could have higher risks of ingesting toxic levels of QT prolonging agents accidently. Routine monitoring of electrolytes in addition to a baseline and follow-up electrocardiograms are important for monitoring patients who are on QT prolonging medications, especially in combination with medications that may alter electrolytes. ECG monitoring after antidepressant initiation varied in the reviewed studies and the package insert for citalopram recommends periodic ECG monitoring after initiation. Given the increased risk of QTc prolongation in older adults with multiple medications and comorbidities, it is important for clinicians to recognize that periodic ECG monitoring is important for older adults who are newly started on an antidepressant.

Conclusion

Available data indicate that TCAs and citalopram pose the greatest risk for QT prolongation in older adults whereas the other SSRIs and SNRIs do not appear to pose any significant risk on their own. Data are lacking in other antidepressants, including bupropion, vilazodone, and levomilnacipran; however, it does not appear that bupropion prolongs the QT interval, based on case reports in nonelderly patients and overdoses. Treating depression in the elderly requires careful consideration of comorbidities, hepatic and renal function, and concomitant drug therapy. Additionally, clinicians should adhere to hospital and clinic guidelines when considering monitoring parameters. Current guidelines by the American Heart Association recommend monitoring a baseline QTc before initiating any agent that may prolong the QTc interval, at the onset of any new bradyarrhythmias, severe hypokalemia or hypomagnesemia, or over dosages of known proarrhythmic pharmacotherapy agents.

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Conflict of interest statement

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