No Association Between Trazodone and Corrected-QT Prolongation in Older Adults

To the Editors:

Recent interest has developed in repurposing trazodone, a tetracyclic selective 5-HT2 receptor antagonist and reuptake inhibitor, for treating Alzheimer disease based on associations between slow-wave sleep (SWS), amyloid-β aggregation, and cognition.[1] Trazodone is frequently prescribed off-label to treat primary or secondary insomnia and more recently for behavioral and psychological symptoms of dementia (BPSD).[2] Two recent clinical studies reported mixed effects of trazodone on cognition. Long-term use of trazodone was associated with delayed cognitive decline in a small sample of 25 patients with Alzheimer disease, mild cognitive impairment, or normal cognition.[3] However, a retrospective cohort study failed to show reduced risk of dementia in trazodone users compared with individuals taking other antidepressants.[4] As evidence of potential benefits of trazodone on dementia risk and other off-label conditions emerges, it is critical that we systematically evaluate the safety profile of trazodone in the geriatric population as pharmacokinetics and tolerability are impacted by aging.[5] Here we focused on the risk of corrected-QT (QTc) prolongation due to trazodone in geriatric patients in a real-world clinical setting.

Although trazodone is clinically considered to have a favorable cardiovascular safety profile, at clinically relevant concentrations in vitro, it demonstrates potent dose-dependent inhibition of human ether-a-go-go related gene (hERG) potassium channels, which correlates with prolongation of QT.[6–9] QTc prolongation on electrocardiogram (ECG) is a risk marker for the potentially fatal arrhythmia torsades de pointes (TdP) and can be caused by a wide range of medications, including psychotropic agents.[10] In addition to polypharmacy, older adults are at increased risk of QTc prolongation owing to advanced age and medical comorbidities such as cardiovascular disease and electrolyte disturbances.[11] Systematic investigations of risk of QTc prolongation due to trazodone in clinical populations are lacking. In a study of 36 healthy individuals, a single dose of trazodone (100 mg) resulted in a 6.9-millisecond increase in QTc 1 hour later.[12] Another study of 8 healthy males aged 23 to 27 years showed a QTc increase of 20 to 30 milliseconds after administration of a single dose of trazodone (150 mg).[13] The clinical significance of these findings is unclear.

Development of TdP with trazodone has been reported only in the presence of additional risk factors or overdose in older adults. A population-based study of various psychotropic medications in adults aged 55 years and older reported no increased risk of QTc prolongation due to trazodone, but the sample included only 3 trazodone users.[14] In the current study, we sought to examine the association between trazodone and QTc in older adults by reviewing electronic health records (Meditech) over a 7-year period (April 2008 to July 2015) from inpatient, nursing home, and rehabilitation settings in a large geriatric health care center (Baycrest, University of Toronto).

TABLE 1. Baseline Characteristics of the Study Sample

	Trazodone (N = 81)
Exposure information	
Minimum dose, mg	12.5
Maximum dose, mg	300
High dose, n (%)	35 (43.2)
Outcome information	
QTc overall, mean (SD)	438.5 (34.5)
QTc in males, mean (SD)	446.7 (35.0)
QTc in females, mean (SD)	430.4 (32.6)
Covariate information	
Age, mean (SD), y	79.8 (10.1)
Female sex, n (%)	41 (50.6)
Clinical setting, n (%)	
Inpatient, medical	10 (12.4)
Long-term care	24 (29.6)
Outpatient	1 (1.2)
Inpatient, psychiatry	7 (8.6)
Rehabilitation	20 (24.7)
Behavioral neurology unit	19 (23.5)
Heart disease, n (%)	35 (43.2)
Coronary artery disease/left ventricular hypertrophy	30 (37.0)
Congestive heart failure	15 (18.5)
History of myocardial infarction	14 (17.3)
Estimated renal clearance, mean (SD), mL/min	52.8 (23.5)
Electrolyte abnormalities, n (%)	5 (6.2)
Hypokalemia	2 (2.5)
Hypomagnesemia	1 (1.2)
Hypocalcemia	2 (2.5)
Dementia, n (%)	
No dementia	30 (37.0)
Dementia	46 (56.8)
Diagnosis unclear	5 (6.2)
Psychotropic medications, n (%)	47 (58.0)
Other antidepressants*	23 (28.4)
Antipsychotics†	28 (34.6)
Lithium	1 (1.2)
Cholinesterase inhibitors‡	7 (8.6)
Nonpsychotropic medications, n (%)	51 (63.0)
Anti-arrhythmic drugs§	7 (8.6)
Anti-infectious‖	11 (13.6)
Bronchodilators¶	7 (8.6)
Gastrointestinal drugs#	32 (39.5)
Diuretics**	25 (30.9)
Other medications††	4 (4.9)
Indication	
Depression, unipolar	3 (3.7)
Depression, bipolar	0 (0.0)
Anxiety	2 (2.5)
BPSD‡‡	34 (42.0)
Insomnia unexplained by other psychiatric condition	34 (42.0)
Other	3 (3.7)
Unknown	5 (6.2)

*Amitriptyline, bupropion, doxepine, duloxetine, fluoxetine, fluvoxamine, mirtazapine, moclobemide, nortriptyline, paroxetine, sertraline, and venlafaxine.

†Aripriprazole, chlopromazine, clozapine, fluphnazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

‡Donepezil and galantamine.

§Amiodarone, diltiazem, disopyramide, dronedarone, procainamide, propafenone, quinidine, sotalol, and verapamil.

‖Amantadine, azythromycin, ciprofloxacin, clarythromycin, erythromycin, levofloxacin, moxifloxacin, and trimethoprim-sulfamethoxazole.

¶Salbutamol and salmeterol.

#Pantoprazole, domperidone, and cisapride.

**Furosemide, hydrochlorothiazide, and indapamide.

††Corrected QT prolonging medications that did not fit in the above categories: diphenhydramine, hydroxyzine, methadone, nicardipine, tamoxifen, and tolterodine.

‡‡Includes depression in patients with dementia diagnosis.

Electronic health records were used to search medical orders for the terms *trazodone* and *ECG*.

Patients on trazodone with ECG data within 24 hours to 90 days[15] of initiation or dosage change were included in analyses based on evidence that ECG changes may occur as early as 24 to 48 hours after administration of psychotropic medications.[12] Those with atrial fibrillation were excluded. The primary outcome was QTc interval reported using a standard 12-lead ECG after initiation or dose change in trazodone. Secondary outcomes were TdP and sudden cardiac death (SCD). Univariable and multivariable linear regressions were used to assess the association between trazodone dosage and QTc interval. Multivariable models retained age, sex, and covariates (heart disease, estimated renal clearance, electrolyte abnormalities, antipsychotics, mood and cholinesterase drugs, and nonpsychotropic medications identified using the Arizona Center for Education and Research on Therapeutics database, supplemented by Pubmed search and consultation with Pharmacy), if they were significant at $P < 0.10$ in univariable analyses. Sensitivity analyses excluded patients with (1) ECG less than or equal to 7 days of medication initiation or dose change and (2) dementia.

Demographic and clinical characteristics are presented in Table 1. Of the 1630 patients taking daily trazodone (all 60+ years of age), 99 patients had ECGs that met eligibility criteria but 18 had atrial fibrillation; thus, the final sample included 81 patients (41 females, 56.8% with dementia). Fifty-eight percent were taking additional psychotropic medications. Sixty-three percent of the sample were taking nonpsychotropic QTc prolonging medications. Regression analyses showed no significant association between trazodone and QTc interval (adjusted $\beta = 0.03$, $P = 0.64$). Among covariates, male sex ($\beta = 16.31$, $P = 0.03$) was significantly associated with QTc in univariable, but not multivariable analyses. No other covariates were statistically significant. Sensitivity analyses did not alter the findings. No cases of TdP were identified. Two cases of SCD were identified; however, one had underlying cardiac disease and both had documented medical instability before death.

To our knowledge, this is the first study to investigate the association between trazodone and incidence of QTc prolongation in a general geriatric patient population. This retrospective review of electronic health records at a geriatric health care center did not find an association between trazodone and QTc interval or increased risk of SCD. The current findings of a lack of association between trazodone and QTc are in line with a previous negative finding in a population-based study of antidepressant use, although the sample included only 3 trazodone users over age of 55 years.[14]

A number of caveats must be noted. Our negative findings may be explained by inadequate statistical power, although the *P* values for trazodone as a predictor were quite large, ranging from 0.34 to 0.64 in multivariable analyses. Furthermore, despite the small sample size, male sex emerged as a statistically significant predictor of QTc in univariable analyses. Female sex is known to be a risk factor for QTc prolongation,[11,16] but other cohort studies of older adult populations report increased prevalence of prolonged QTc in older males.[17,18] Other limitations to the current study include its retrospective design. A within-subject methodology comparing QTc before and after trazodone initiation or dose change in the same patient would provide a more definitive analysis. However, very few cases in this real-world sample included an ECG within the eligible time frame before starting trazodone.

Given these study limitations, our findings should be viewed with caution. This study failed to detect an association between trazodone and QTc interval at dosages used in a real-world clinical setting of geriatric patients with multiple risk factors for QTc prolongation. In the absence of other empirical evidence, the current findings should provide clinicians with some guidance when making risk-benefit assessments for off-label use of trazodone.

ACKNOWLEDGMENT

Gabrielle Crépeau-Gendron is co-senior author.

This study was funded by the Baycrest Psychiatry Academic Development Fund.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

The views expressed in the submitted article are from the authors only and are not an official position of their institutions.

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Lithium Therapy Associated With Renal and Upper and Lower Urinary Tract Tumors

Results From a Retrospective Single-Center Analysis

To the Editors:

In February, 2015, the European Medicines Agency communicated that the current evidence is sufficient to conclude that long-term use (>10 years) of lithium may induce microcysts, oncocytomas, and collecting duct renal carcinomas.[1] Thereupon, marketing authorization holders of lithium containing medical products were requested to amend the product information accordingly.[1] The currently available epidemiological studies regarding the association between lithium therapy (LT) and renal and urinary tract tumors, however, differ significantly in terms of included tumors, methodology, and results.[2–4] Thus, an adequate evaluation of the relation between (long-term) LT and the risk for renal und urinary tract tumors is currently not possible. The mechanisms underlying lithium-induced nephrotoxicity in general and lithium-associated oncogenesis in the kidney and the upper and lower urinary tract in particular are not completely understood.[2,5] Lithium exerts possible oncogenic effects merely in the intracellular space and primarily enters the cells of the kidney via the amiloride-sensitive epithelial sodium channel (ENaC).[6–8] The urothelium of renal pelvis, ureter, bladder, and urethra also expresses ENaCs,[9–13] thus making these tissues theoretically also susceptible to lithium-associated oncogenesis. However, the aforementioned epidemiological studies have not considered the lower urinary tract (urethra and bladder).[2–4] In addition, the ENaC consists of 3 different subunits (α, β, γ) and a fourth so-called δ subunit, whose function is unknown.[14,15] These subunits are expressed differently in kidneys and the urothelium of renal pelvis, ureter, bladder, and urethra (eg, stronger expression of α, β, and γ subunits in the kidney than in the urothelium of the bladder).[9,11] Therefore, there may be a relation between the tissue-specific expression of ENaCs and the tissue-specific susceptibility regarding lithium-associated oncogenesis. Taking into account these aspects, we performed an exploratory retrospective, single-center analysis of patients with malignant and benign renal and upper and lower urinary tract tumors to (1) determine the prevalence of LT and (2) investigate if the prevalence of LT varies significantly between different tumor entities as an indication of a possible relation between the tissue-specific susceptibility regarding lithium-associated oncogenesis and the tissue-specific expression of ENaCs.

The study protocol was introduced to the local ethics committee/human subjects committee of Ulm University and received approval. All patients receiving treatment in the Department of Urology at the University Hospital of Ulm between January 1, 2006, and December 31, 2015, owing to 1 or more of the following index tumor groups according to *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*), were included for further data acquisition: malignant neoplasm of kidney, except renal pelvis (*ICD-10* C64), malignant neoplasm of renal pelvis (*ICD-10* C65), malignant neoplasm of ureter (*ICD-10* C66), malignant neoplasm of bladder (*ICD-10* C67), malignant neoplasm of other and unspecified urinary organs (*ICD-10* C68), and benign neoplasm of urinary organs (*ICD-10* D30). (Because of the high number of cases of malignant bladder tumors treated between January 1, 2006, and December 31, 2015, resulting in overrepresentation of these entity [1712 malignant bladder tumors vs 904 malignant renal tumors], the reference period for this tumor entity was later restricted to January 1, 2010, and December 31, 2015, resulting in 951 malignant bladder tumors.) Patients with age less than 18 years at the time of treatment at the Department of Urology owing to 1 of the previously mentioned index tumors were excluded. The clinic's internal digital patient database was screened for eligible patients by using the previously mentioned *ICD-10* codes. Digital files of patients identified in this procedure were checked by hand for the presence of the previously mentioned inclusion and exclusion criteria. The following data were extracted from the digital patient files: age (at the time of diagnosis of the index tumor based on the date of the report on the histopathological findings or the date of the first doctor's report listing respective diagnosis), sex, exposure to lithium (yes/no) and period of exposure to lithium, type of tumor, histological subtype of tumor, and risk factors for the development of renal and upper and lower urinary tract tumors: body height and weight (calculation of the body mass index using these parameters), smoking status, arterial hypertension, estimated glomerular filtration rate (measurement before the surgical procedure due to the respective index tumor, as documented in the digital patient files or calculated based on the Chronic Kidney Disease Epidemiology Collaboration formula[16]), exposure to aromatic amines, use of phenacetin-containing analgesics, chronic urinary tract infection, von-Hippel-Lindau disease, and radiotherapy of the pelvis. Exposure to lithium before diagnosis of 1 of the index tumors was defined as presence of correspondent information in the digital patient files and/or written or oral statements by the patient. Information regarding the period of exposure to lithium was also retrieved from the digital patient files or requested directly from the patient. If the digital patient files did not provide sufficient information regarding prior exposure to lithium, the patients were contacted by