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Mirtazapine's effect on the QT interval in medically hospitalized patients

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Abstract

Introduction: Mirtazapine is generally well tolerated in medically ill patients with and without formal psychiatric comorbidity to target sleep, appetite, nausea, and pain. However, there is little data regarding mirtazapine's potential to prolong the corrected QT interval (QTc) in this population.

Methods: From a retrospective cohort of patients hospitalized on a variety of medical units for whom a psychiatric consult recommended mirtazapine, electrocardiogram (ECG) data were extracted for ECGs obtained up to 3 days before and 6 days after the initial consult. Descriptive statistics were used to characterize the QTc changes and adverse cardiac outcomes, including incident ventricular tachycardia, torsades de pointes, and sudden cardiac death. Multiple linear regression models were completed to assess the effect of potential confounding variables on QTc changes.

Results: Complete premirtazapine and postmirtazapine ECG data were available for 61 patients, and the average change in QTc was −0.31 ms (SD = 36.62 ms). No incidental adverse cardiac outcomes were found. QTc changes were not significantly affected by patient age and sex, initial and maximum mirtazapine dose, days between ECGs, number of concomitant QTc prolonging medications, Charlson comorbidity scores, and electrolyte abnormalities. Due to incomplete potassium, magnesium, and ionized calcium data, electrolytes were excluded from the final regression model.

Discussion: Despite the limitations of this retrospective study, these data suggest that modest doses of mirtazapine may not significantly affect the QTc in medically ill patients. Retrospective cohorts are more feasibly analyzed, but prospective controlled trials could more systematically assess QTc changes with higher doses of mirtazapine in medical settings.

Keywords: consultation liaison psychiatry, antidepressants, psychopharmacology, mirtazapine, QT prolongation, cardiology

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Introduction

Mirtazapine has a unique antidepressant mechanism through the antagonism of serotonin receptors 5-HT2 and 5-HT3 as well as adrenergic alpha 2-autoreceptors and alpha 2-heteroreceptors. This results in the release of norepinephrine and enhances 5-HT1A–mediated serotonergic transmission.[1] Mirtazapine's beneficial effects on sleep and increased appetite are mediated by histaminic H1 receptor antagonism, and nausea is reduced by 5-HT3

receptor antagonism. With these possible benefits, mirtazapine may often be recommended by a consult/liaison psychiatric service for medically ill patients. Psychiatrists must also consider the potential for prolongation of the corrected QT interval (QTc) as significant prolongation and subsequent fatal arrhythmias are more likely in this population.

Mirtazapine's prescribing information indicates minimal risk of prolonged QTc.[2] The supporting 6-week placebo-controlled trial for depression analyzed electrocardiograms (ECGs) for 338 outpatients receiving mirtazapine and 261 patients receiving placebo. In this population, an increase in the QTc beyond 500 ms was not observed among mirtazapine-treated patients, and the mean change in QTc was +1.6 ms for mirtazapine and –3.1 ms for placebo.[2] These data, however, may not apply to medically ill patients, who are at higher risk of QTc prolongation due to electrolyte abnormalities, drug interactions, and cardiopulmonary comorbidities.

Few studies of QTc changes in medically ill patients receiving mirtazapine have been conducted. One randomized controlled trial[3] of 91 patients demonstrated efficacy and safety for patients with depression after myocardial infarction. The 47 patients randomized to mirtazapine did not show a significant increase in the QTc compared to the placebo group. A recent retrospective study[4] of 475 medical inpatients with and without psychiatric comorbidity demonstrated the general tolerability of mirtazapine for the improvement of sleep, appetite, and nausea. Alternatively, a cohort study[5] including 214 072 patients taking mirtazapine reported a slight but significant increase (hazard ratio = 1.26, 95% confidence interval = 1.11–1.42) in sudden cardiac death and ventricular arrhythmia compared to paroxetine. The authors noted that mirtazapine was more commonly prescribed to elderly patients with greater medical comorbidity and were hesitant to interpret the association as causal. To more thoroughly characterize the QTc changes for medical inpatients started on mirtazapine, a secondary analysis was conducted in the retrospective cohort of 475 patients.

Methods

This project was approved by the Mayo Clinic Institutional Review Board. Patients from the cohort assessed in a previously published study[4] were used in this analysis. Pharmacy records were obtained from January 1, 2010, to June 30, 2015, to identify patients in a nonpsychiatric inpatient setting who were dispensed at least 1 dose of mirtazapine during hospitalization as recommended by a consultation liaison psychiatrist. The relevant medical records were reviewed for 1 ECG performed within 3 days of the initial psychiatric consult and another ECG within 6 days after the initial psychiatric consult. This timeline allows for the inclusion of a baseline ECG that adequately reflects the patient's frequently changing medical status and for the second ECG to be gathered when mirtazapine has nearly reached steady state. The initial psychiatric consult was used as a proxy for the first day of mirtazapine initiation. The QTc and rhythm interpretation was recorded for each ECG. The QTc change and days in between ECGs was calculated. Rhythm interpretations were reviewed for new ventricular tachycardia, torsades de pointes (TdP), and sudden cardiac death. Potential confounders, including initial and maximum mirtazapine dose, patient age and sex, number of concomitant QT prolonging medications, comorbidities as assessed by Charlson comorbidity scores, and electrolytes (potassium, magnesium, and ionized calcium) on the same day of the second ECG, were recorded when available.

QTc prolonging medications were identified using a reputable and regularly updated source, (http://crediblemeds.org/; AZCERT, Inc, Oro Valley, AZ) and all risk categories were included. Charlson comorbidity index scores were electronically obtained and scored on severity- and age-weighted sum of disease. This is a weighted index used to predict risk of death within 1 year of hospitalization for patients with specific comorbid conditions. Comorbidities are scored 1 to 6 based on relative risk of death and points added for every decade over 40 years of age. Finally, if patients had multiple electrolyte values drawn, the lowest value was used to capture the highest potential for QTc prolongation.

Descriptive statistics were used to report results as means with standard deviations or proportions when appropriate. Finally, statistical analyses were conducted to investigate whether the variance in QTc changes was affected by any of the aforementioned potential confounders. This was completed using multiple linear regression models with continuous and categorical variables when appropriate.

Results

Of the original 475 patients with a psychiatric consult recommending mirtazapine, 61 patients had ECGs performed within 3 days before and 6 days after the initial consult recommending mirtazapine. These 61 patients had a mean age of 64.5 ± 14.3 years, and 55.7% were male. Mirtazapine was initiated at a mean dose of 9.8 mg (±3.6 mg) and titrated to a mean maximal dose of 13.5 mg (±6.3 mg), reflecting a general trend of initiating at 7.5 mg nightly and increasing to 15 mg nightly as clinically indicated. Mirtazapine was not discontinued in any of the 61 patients, and no incidental cardiac outcomes were found. The mean QTc change from baseline was –0.31 ms

TABLE 1: Cohort description of the study (sex = 55.7% male, 100% data available)

Cohort Description	Mean	SD	Data Available, %
Age, y	64.5	14.3	100
Initial dose, mg	9.8	3.6	100
Maximum dose, mg	13.5	6.3	100
Time between electrocardiograms, d	4.4	2.0	100
Charlson comorbidity scores (age and severity weighted)	3.8	2.8	100
No. concomitant QT-prolonging medications	3.2	1.9	100
Lowest potassium, mmol/L, reference range = 3.6 to 5.2	4.1	0.6	87
Lowest magnesium, mg/dL, reference range = 1.7 to 2.3	1.8	0.3	54
Lowest ionized calcium, mg/dL, reference range = 4.65 to 5.30	4.6	0.6	23
QTc change, ms	–0.31	36.62	100

(±36.62 ms) with a mean first QTc of 468.57 ms (±42.52 ms) and a mean second QTc of 468.26 ms (±37.56 ms). A total of 15 patients were found to have a QTc prolongation of 20 ms or more from baseline, 6 patients had a QTc prolongation of 40 ms or more, and 9 patients had a second QTc of more than 500 ms. These results and the cohort description are summarized in Table 1.

A mean of 4.4 days (±2.0 days) elapsed between ECGs. The mean age- and severity-weighted Charlson comorbidity score was 3.8 (±2.8), and the mean number of concomitant QT prolonging medications was 3.2 (±1.9). Although all the aforementioned data were available for all 61 patients, the electrolyte data were less complete. Potassium, magnesium, and ionized calcium values collected within 1 day of the second ECG were available for 87%, 54%, and 23% of patients, respectively. The mean lowest potassium was 4.1 mmol/L (±0.6, reference range = 3.6 to 5.2 mmol/L), the mean lowest magnesium was 1.8 mg/dL (±0.3, reference range = 1.7 to 2.3 mg/dL), and the mean lowest calcium was 4.6 mg/dL (±0.6, reference range = 4.65 to 5.30 mg/dL).

Given the large standard deviation in QTc changes, multiple linear regression models were used to model the effects of potential cofounders. Days between ECGs, initial and maximum mirtazapine dose, patient age, number of QT-prolonging medications, Charlson comorbidity scores, and electrolytes (potassium, magnesium, and ionized calcium) were modeled as continuous variables. Patient sex was modeled as a categorical variable. Given the limited number of available ionized calcium values, the available data were modeled 1 at a time and not found to be significant. Similarly, potassium and magnesium values were not found to significantly affect QTc changes, so they were also excluded from the final model to strengthen power. In the final model without electrolytes (n = 61), none of the investigated variables significantly affected QTc changes (Table 2).

TABLE 2: Final model—multiple linear regression model without electrolytes

Variable	Estimate	SE	*P* Value
Age (yes)	–0.25	0.45	.58
Sex (female)	–7.11	6.05	.25
Initial mirtazapine dose, mg	1.20	1.82	.51
Maximum mirtazapine dose, mg	–0.27	0.94	.78
Days between electrocardiograms	–3.98	3.10	.21
Charlson comorbidity scores (age and severity weighted)	0.96	2.48	.70
No. concomitant QT-prolonging medications	0.08	3.67	.98

Discussion and Conclusion

Risk factors for QTc prolongation and TdP are more prevalent in medically hospitalized patients. These risk factors include congenital long QT syndrome, increased age, female sex, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, congestive heart failure, valvular disease, cardiomyopathy, recent myocardial infarction, and coprescription of multiple QT-prolonging medications.[6-8] The direct mechanism of drug-induced QTc prolongation appears to be primarily mediated by blocking the delayed rectifier potassium currents in cardiac myocytes.[9] Indirectly, drugs can also prolong the QTc by interfering with the metabolism of other drugs that delay cardiac repolarization. Medically ill patients are exposed to medications such as anti-infective, antiemetic, and antiarrhythmic agents known to prolong the QTc. Monitoring all these factors simultaneously can prove difficult for consult-liaison psychiatrists, highlighting the importance of familiarity with medications at relatively higher or lower risk of QTc prolongation and TdP.

These data add to the literature supporting the safety of mirtazapine in medically hospitalized patients as no incidental cases of ventricular tachycardia, TdP, or sudden cardiac death were found. Even though the average QTc was greater than 460 ms, the average change in QTc was close to zero. Despite the large standard deviation in QTc changes, none of the investigated confounding variables that are known to affect QTc intervals were found to have significant effects. This could possibly be explained by the

inclusion of all medications with potential risk of QTc prolongation and the use of Charlson comorbidity scores to control for medical severity. Perhaps using only medications known to increase risk of QTc prolongation and more specific control of cardiopulmonary comorbidities would have yielded significant results. The small sample size, lack of data available for electrolytes, modest reductions in electrolyte values for those that were available, and relatively low doses of mirtazapine may also have contributed to the insignificant effects of confounders.

Most classes of psychotropics, including antihistamines, antidepressants, and antipsychotics, are associated with QTc prolongation and TdP. When comparing mirtazapine to other psychotropics used in the medically ill, haloperidol is the most commonly reported psychotropic associated with TdP. Torsades de pointes is estimated to occur in 0.14% of patients reporting adverse effects with haloperidol, and 6 fatalities have been reported.[10] Additionally, citalopram, ziprasidone, and thioridazine are noted to carry greater propensity for QTc prolongation,[11] but other drugs used more frequently for sleep carry risks as well. Comprehensive reviews of drug-induced QTc prolongation and TdP have been undertaken previously[6-8,10-12] although other side effects may affect a clinician's choice of medications in the medically ill.

Diphenhydramine and doxepin have both been associated with prolonged QTc and TdP but also carry a significant anticholinergic burden.[10] Quetiapine may cause limiting orthostasis, is associated with sudden cardiac death in retrospective cohorts, slightly prolongs the QTc, and has been reported to be associated with TdP in overdose.[11] Trazodone overdoses have been reported to mildly prolong the QTc[12] but also carry the risk of orthostasis. Without anticholinergic burden or significant orthostasis, low doses of mirtazapine may offer clinicians a gentler option for addressing poor sleep, low appetite, and nausea in the medically ill.

This study was limited by its retrospective nature and small sample size, which resulted from the limited availability of timely ECGs and electrolyte data. Additionally, the use of mirtazapine primarily at the lower end of the dosing range limits the generalizability of these conclusions to severely depressed or anxious medical patients. It would be useful to study ill cardiovascular patients with psychiatric complications that require higher doses of mirtazapine. As such, further controlled trials are needed to systematically assess mirtazapine's potential to prolong the QTc and cause adverse cardiac outcomes in medically ill patients.

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