# Quetiapine, QTc interval prolongation, and *torsade de pointes*: a review of case reports

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***Abstract:*** Recently, both the manufacturer of quetiapine and the US Food and Drug Administration warned healthcare providers and patients about quetiapine-induced QTc interval prolongation and *torsade de pointes* (*TdP*) when using this drug within the approved labeling.

We reviewed the case-report literature and found 12 case reports of QTc interval prolongation in the setting of quetiapine administration. There were no cases of quetiapine-induced *TdP* or sudden cardiac death (SCD) among patients using quetiapine appropriately and free of additional risk factors for QTc interval prolongation and *TdP*. Among the 12 case reports risk factors included female sex (nine cases), coadministration of a drug associated with QTc interval prolongation (eight cases), hypokalemia or hypomagnesemia (six cases) quetiapine overdose (five cases), cardiac problems (four cases), and coadministration of cytochrome P450 3A4 inhibitors (two cases). There were four cases of *TdP*. As drug-induced *TdP* is a rare event, prospective studies to evaluate the risk factors associated with QTc prolongation and *TdP* are difficult to design, would be very costly, and would require very large samples to capture *TdP* rather than its surrogate markers. Furthermore, conventional statistical methods may not apply to studies of *TdP*, which is rare and an 'outlier' manifestation of QTc prolongation. We urge drug manufacturers and regulatory agencies to periodically publish full case reports of psychotropic drug-induced QTc interval prolongation, *TdP*, and SCD so that clinicians and investigators may better understand the clinical implications of prescribing such drugs as quetiapine.

***Keywords:*** case reports, drug-induced QTc interval prolongation, quetiapine, risk factors, *torsade de pointes*

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## Introduction

Quetiapine is a second-generation antipsychotic widely used for various psychotic and mood disorders. In July 2011, the US Food and Drug Administration (FDA) directed AstraZeneca to add a warning to the quetiapine (Seroquel, AstraZeneca, Wilmington, USA) labeling about QT interval prolongation and the potential to induce *torsade de pointes* (*TdP*). These recommendations were implemented the following year [Astrazeneca Quetiapine (Seroquel) Prescribing Information, 2013]. This warning was based on postmarketing reports of QT interval prolongation among patients who overdosed on quetiapine, had a concurrent illness, or received medications known to cause electrolyte abnormalities or to cause QT interval prolongation [Anonymous, 2011]. AstraZeneca identified certain QTc interval prolonging drugs that should not be coadministered with quetiapine, including class 1-A antiarrhythmics (e.g. quinidine, procainamide) or class III antiarrhythmics (e.g. amiodarone, sotalol); antipsychotic drugs (e.g. ziprasidone, chlorpromazine, thioridazine); antibiotics (e.g. gatifloxacin, moxifloxacin); or any other class of drugs known to prolong the QTc interval (e.g. pentamidine, levomethadyl acetate, methadone) [Astrazeneca Quetiapine (Seroquel) Prescribing Information, 2013]. The warning was not based on a thorough QT/QTc study [Darpo,

2010]. AstraZeneca and the FDA did not provide any new information about quetiapine's capacity to induce QTc interval prolongation sufficient to place the patient at increased risk for *TdP* when used as monotherapy in a population who were not at risk for QTc interval prolongation or receiving other medications that may prolong the QTc interval.

Recently, we published our approach to case report material interpretation for citalopram [Vieweg *et al.* 2012] and methadone [Vieweg *et al.* 2013] and their impact on QTc interval prolongation and *TdP*. We argued that risk factors for QTc interval prolongation and *TdP* are more predictive of drug-associated serious electrocardiographic (EKG) changes than drug administration alone. We now extend our review to quetiapine.

## Methods

On 28 October 2012, we entered 'quetiapine and qt prolongation' (35 articles) and then 'quetiapine and torsade' (six articles) into PubMed with no time range. We also reviewed reports from our files and the files of AstraZeneca (personal communication).

## Results

We identified 12 published case reports (Table 1) of quetiapine-associated QTc interval prolongation and *TdP* in which simultaneous QTc interval measurement and quetiapine dose were available. Nine subjects were women (age range 31–77 years) and three subjects were men (age range 14–41 years). Risk factors for each case report appear in Table 1. Appendix A (available in online publication) provides case report details. No case reports demonstrated quetiapine-associated QTc interval prolongation without either quetiapine overdose or associated well known risk factors for QTc interval prolongation and *TdP* [Vieweg *et al.* 2009, 2011]. Using nonparametric statistics ($n$ = 12, Table 1), we found no significant correlation between QTc interval and quetiapine dose (Kendall's $\tau b = 0.290$, $p = 0.192$; Spearman's $\rho = 0.308$, $p = 0.330$). We did not perform a case control study and could not find any comparable analyses in the literature.

## Discussion

The major finding of our review is the high prevalence of the well-established risk factors [Bednar *et al.* 2001; Viskin *et al.* 2003; Beach *et al.* 2013] for acquired QTc prolongation in these case reports (Table 1). Nine of the 12 cases were women. Coadministration of another drug associated with QTc interval prolongation appeared in six cases. Hypokalemia or hypomagnesemia appeared in six cases. Quetiapine overdose appeared in five cases. Issues related to cytochrome P450 3A4 inhibition possibly causing high plasma quetiapine concentrations appeared in two cases. Four patients had significant cardiac disease including valvular problems, congestive heart failure, or arrhythmia. Polymorphic ventricular tachycardia of the *TdP* type appeared in 4 of the 12 cases; all these cases had multiple risk factors for QTc interval prolongation and *TdP* (Table 1). Overall, the risk factors of concern in patients taking quetiapine identified in our review were consistent with those identified in the quetiapine labeling information on direction from the FDA.

A culprit drug is only 1 of over 20 potential risk factors associated with acquired QTc prolongation [Bednar *et al.* 2001; Viskin *et al.* 2003; Beach *et al.* 2013]. In data from the Third National Health and Nutrition Examination Survey on 8561 adults older than 40 years [Benoit *et al.* 2005], age, female sex, hypocalcemia (men), hypokalemia (women), and a history of thyroid disease and myocardial infarction (men) were associated with a prolonged QTc interval. In addition, taking QT-prolonging medications in the past month increased the odds of prolonged QTc interval more than twofold in both men and women. Tisdale and colleagues [Tisdale *et al.* 2013] studied 900 consecutive patients admitted to cardiac units of a tertiary care hospital. Independent predictors of QTc prolongation included female sex, age over 68 years, diagnosis of myocardial infarction, septic shock, left ventricular dysfunction, administration of a QT-prolonging drug, at least two QT-prolonging drugs or loop diuretic, serum potassium less than 3.5 mEq/liter, and admitting QTc greater than 450 ms. In a study of HIV-infected patients [Reinsch *et al.* 2009], female sex, diabetes mellitus, and arterial hypertension were associated with prolonged QTc. Yet in another study of ibutilide (a class III antiarrhythmic known to prolong QTc interval) in 253 normal volunteers aged 18–40 years [Kannankeril *et al.* 2011], overweight and obesity was associated with QTc prolongation in both men and women without any sex differences. These data highlight that the risk factors may vary by the drug and the population being studied.

**Table 1.** Case report risk factors linked to quetiapine-associated QTc interval prolongation and *TdP*. Case 1 was also reported by Hustey [Hustey, 1999]. The case reports did not describe how the QTc interval was measured.

| Case | Age (years), sex (M/F) | QTc (ms), *TdP* (yes/no) | Quetiapine (mg) | Risk factors |
|---|---|---|---|---|
| 1 [Gajwani *et al.* 2000] | 19M | 710 **No** | 9600 | Quetiapine overdose, P4503A4 metabolic inhibitor (fluvoxamine), hypokalemia |
| 2 [Beelen *et al.* 2001] | 31F | 537 **No** | 2000 | Female sex, quetiapine overdose, also taking low-dose risperidone |
| 3 [Furst *et al.* 2002] | 46F | 569 No | 800 | Female sex, therapeutic quetiapine, possible competitive P4503A4 metabolic inhibition (lovastatin) |
| 4 [Gupta *et al.* 2003] | 50F | 480 **No** | 400 | Female sex, therapeutic quetiapine, citalopram 40 mg/day |
| 5 [Kurth and Maguire *al.* 2004] | 14M | 500 **No** | 1900 | Quetiapine overdose |
| 6 [Vieweg *et al.* 2005] | 45F | 548 **Yes** | 100 | Female sex, therapeutic quetiapine, hypomagnesemia, hypocalcemia, also taking escitalopram, cardiac problems (hypertension, ventricular fibrillation) |
| 7 [Strachan and Benoff, 2006] | 41M | 684 **No** | 4500 | Quetiapine overdose |
| 8 [Bodmer *et al.* 2008] | 34F | 620 **No** | 3000 | Female sex, quetiapine overdose |
| 9 [Digby *et al.* 2010] | 58F | 720 **Yes** | 350 | Female sex, therapeutic quetiapine, cardiac problems (hypertension, heart failure), also taking citalopram, hypokalemia |
| 10 [Aghaienia *et al.* 2011] | 63F | 525 **No** | 800 | Female sex, therapeutic quetiapine, diabetes mellitus, past history of ziprasidone-induced QTc interval prolongation, hypokalemia |
| 11 [Digby *et al.* 2011] | 67F | 610 **Yes** | 200 | Female sex, therapeutic quetiapine, cardiac problems (coronary artery disease, atrial fibrillation, prosthetic tricuspid valve replacement, epicardial pacemaker), hypokalemia, hypomagnesemia, escitalopram, furosemide |
| 12 [Digby *et al.* 2011] | 77F | 529 **Yes** | 25 | Female sex, therapeutic quetiapine, cardiac (hypertension, aortic stenosis, and mitral stenosis), hypokalemia, hypomagnesemia, citalopram, amitriptyline, furosemide |

The majority of drugs linked to QTc interval prolongation and *TdP* are linked to pharmacological blockade of *hERG* (human-Ether-a-go-Related Gene) potassium channels, which mediate the rapid delayed rectifier ($I_{Kr}$) current and thereby influence ventricular repolarization [Hancox *et al.* 2008]. Quetiapine has been linked to hERG channel blockade with a half-maximal inhibitory concentration of 5.765 μM [Kongsamut *et al.* 2002]. While the preclinical data (see Hasnain and colleagues for a more in-depth discussion [Hasnain *et al.* 2013]) identify quetiapine to carry the risk of QTc prolongation, clinical data on specific factors that may mediate or potentiate the risk are very limited. Our review provides some information in this regard. Well designed studies are needed to quantify the contribution of established risk factors (e.g. congenital QTc prolongation, hypokalemia, hypomagnesaemia, factors that increase drug levels, and combination of QTc-prolonging drugs), to better define the role of less well established factors (e.g. cardiovascular disease, diabetes mellitus), and to identify the potential contribution of relevant factors identified in studies on other drugs (e.g. overweight/obesity).

Quetiapine is a widely used antipsychotic drug for approved indications, including various psychotic and mood disorders and for off-label purposes including psychosis and agitation associated with dementia or delirium and behavioral symptoms

associated with disorders of conduct in children and adolescents. Literature to guide on the risk of quetiapine-associated QTc prolongation and *TdP* in specific patient populations is lacking. Several patients in the case reports we reviewed had multiple medical problems and at least one patient had delirium. In a small study of 36 adult intensive care unit (ICU) patients with delirium, QTc prolongation was similar for quetiapine and haloperidol (another antipsychotic associated with QTc prolongation) [Devlin *et al.* 2010]. ICU patients are at a very high risk of QTc prolongation [Ng *et al.* 2010] and quetiapine use in this population should be very cautious. Similarly, patients with delirium (including delirium superimposed on dementia) or multiple acute medical problems would be at risk of QTc prolongation either due to existing risk factors (e.g. age, hepatic impairment, cardiac disease etc.) or due to vulnerability to new-onset risk factors (e.g. electrolyte derangements) and use of quetiapine in such patients should take these risk factors into account. Current literature does not guide on EKG-based screening or monitoring of quetiapine-related QTc prolongation but it may have a role when dealing with modifiable risk factors such as electrolyte disturbances or coadministration of QTc-prolonging drugs. The dose of quetiapine can range from 12.5 mg/day to 800 mg/day (or higher as an off-label use), depending on the reason for its use. Literature on the dose–response relationship between quetiapine and QTc prolongation is lacking. All patients (or the family) must be informed of this potential risk when prescribing quetiapine.

The major limitation of our study is that it is based on only 12 case reports. As drug-induced *TdP* is a rare event, prospective studies to study the risk factors associated with QTc prolongation and *TdP* are difficult to design, would be very costly and would require very large samples to capture *TdP* rather than its surrogate markers. Furthermore, conventional statistical methods may not apply to studies of *TdP*, which is rare and an 'outlier' manifestation of QTc prolongation. Readers interested in a more in-depth discussion on this topic should refer to a publication by Hasnain and colleagues [Hasnain *et al.* 2013]. Despite all the limitations inherent in case reports, a case report format may be the most pragmatic approach to help us better understand risk factors distinguishable from therapeutic doses of the drug of interest (in this case, quetiapine) that contribute to or account for drug-associated QTc interval prolongation and *TdP*.

## Conclusion

The risk of QTc prolongation may be minimal when it is used in the recommended therapeutic dose in patients without other risk factors for QTc prolongation. Exposure to supratherapeutic doses of quetiapine, use of quetiapine in situations when its metabolism is compromised, coadministration of other drugs associated with QTc prolongation, and presence of electrolyte derangements associated with arrhythmias would amplify the risk. As with several other drugs, congenital prolonged QTc, female sex, old age, and family history of prolonged QTc would be risk factors for quetiapine-associated QTc prolongation. Presence of cardiac problems such as arrhythmias, heart failure, and valvular problems may add to the risk but the association with specific cardiac problems is less clear. Presence of multiple risk factors would increase the risk of QTc prolongation and *TdP*. Physicians should be aware of these risk factors in making decisions regarding drug choice in order to minimize the risk.

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W Victor Vieweg, MD, an author on this paper, passed away on October 7, 2013 in Charlottesville Virginia. Dr Vieweg who began his career as a Cardiologist later specialized in Psychiatry. He was a prolific researcher especially in the interface of Psychiatry and Medicine, and often ahead of the times in conceptualizing disease and treatment models. In his death, both Psychiatry and Medicine have lost a great scholar and teacher.

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**Appendix A.** Detailed information in case reports of quetiapine administration associated with QTc interval prolongation.

| Year and case report | **Comment** |
|---|---|
| Case 1, 2000 [Gajwani *et al.* 2000] 'QT interval prolongation associated with quetiapine (Seroquel) overdose' | A 19-year-old man ingested 9.6 g of quetiapine (mainly metabolized by cytochrome P450 3A4) in a suicide attempt. He was also taking fluvoxamine that is a cytochrome P450 3A4 inhibitor and this may have increased quetiapine plasma levels. Two hours post overdose, the QTc interval was 581 ms and it progressively increased to 710 ms. *TdP* did not occur. A contributing risk factor for QTc interval prolongation may have been the initial serum potassium of 3.3 mmol/liter. Serum potassium concentration was 4.1 mmol/liter 3 h later. However, it is the cardiac concentration of potassium that best determines the risk of QTc interval prolongation and *TdP* and tissue potassium concentration may not have returned to normal in 3 h. Serum magnesium (1.7 mg/dl) was in the low–normal range (1.7–2.2 mg/dl) and may have contributed to QTc interval prolongation. He was treated with activated charcoal and intravenous administration of magnesium. At 27 h post ingestion, the QTc interval had returned to normal (440 ms). When the QTc interval was prolonged to 710 ms, the ventricular rate was 96 bpm. Quetiapine overdose commonly increases the heart rate and the Bazett formula tends to overestimate the QTc interval at higher heart rates [Indik *et al.* 2006]. However, increased heart rate and the Bazett formula would not alone explain a QTc interval prolongation of 710 ms. Thus, quetiapine overdose was the main reason for QTc interval prolongation in this case |
| Case 2, 2001 [Beelen *et al.* 2001] 'Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone' | A 31-year-old woman overdosed with 2 g of quetiapine in a suicide attempt. She was also taking risperidone 1 mg daily. Two hours post overdose, her QTc interval was prolonged to 537 ms when her heart rate was 95 bpm (plasma quetiapine level 1800 mg/ml, 'therapeutic' values 20–50 ng/ml). *TdP* did not occur. Chemistries including serum electrolytes remained in the normal range. Quetiapine overdose commonly increases the heart rate and at higher heart rates, the Bazett formula tends to overestimate the QTc interval [Indik *et al.* 2006]. The initial risperidone plasma concentration was 6.4 ng/ml and the plasma concentration of 9-hydroxy-risperidone was 19 ng/ml making it highly unlikely that risperidone contributed substantively to QTc interval prolongation. At 18 h post overdose, the QTc interval had returned to normal (401 ms) |

*(Continued)*

**Appendix A.** (Continued)

| Year and case report | **Comment** |
|---|---|
| Case 3, 2002<br>[Furst *et al.* 2002]<br>'Possible association of QTc interval prolongation with coadministration of quetiapine and lovastatin' | A 46-year-old woman with schizophrenia took quetiapine 800 mg and sertraline 100 mg daily. Cholesterol and triglyceride values were found to be elevated and she was prescribed lovastatin 10 mg daily. A routine EKG then showed QTc interval prolongation of 569 ms on a day that she took 20 mg of lovastatin because she had forgotten to take her dose the day before. Six months before starting quetiapine or lovastatin, a routine EKG showed QTc interval of 416 ms (normal). Electrolytes were normal. Lovastatin was reduced to 5 mg daily and an EKG the next day showed a return to baseline QTc interval (424 ms, normal). Two months later, she was switched to niacin because lipids had increased. Subsequent EKGs remained normal.<br>The authors hypothesized that since both quetiapine and lovastatin are metabolized by cytochrome P450 3A4, competitive inhibition led to a rise in quetiapine concentration and QTc interval prolongation. Because sertraline is also metabolized by cytochrome P450 3A4, it potentially may have contributed to elevated quetiapine plasma concentrations. However, in this case the coadministration of quetiapine and sertraline was not associated with QTc interval prolongation.<br>AstraZeneca responded to this publication [Geller *et al.* 2002] and offered a series of observations including uncertainty about how QTc interval prolongation was determined (computer calculation or manual calculation); the potential for increased heart rate to overestimate QTc interval prolongation using the Bazett formula; possible spurious QTc interval measurement; the possibility that sertraline may have caused QTc interval prolongation; and the Pfizer 054 study [Psychopharmacological Drugs Advisory Committee, 2000] showing that a cytochrome P450 3A4 inhibitor coadministered with quetiapine showed no significant change when the Fridericia correction formula [Franz, 2008] was used to calculate the QTc interval.<br>Pierre and colleagues [Pierre *et al.* 2002] (coauthors of case 3) responded to the above observations and concluded that clinicians should be vigilant to possible cardiac arrhythmias when coadministering quetiapine and a cytochrome P450 3A4 inhibitor |
| Case 4, 2003<br>[Gupta *et al.* 2003]<br>'Quetiapine and QTc issues: a case report' | A 50-year-old woman received citalopram 40 mg daily, quetiapine 300 mg daily, fluticasone inhaler, theophylline 400 mg daily, ipratropium inhaler, furosemide 20 mg daily, amlodipine 5 mg daily, and perindopril 8 mg daily to treat schizoaffective disorder and various medical conditions. Quetiapine was increased to 400 mg daily at which time an EKG printout reported QTc interval prolongation of 612 ms. This was checked manually and the measured QTc interval was slightly prolonged at 480 ms. Cardiology consultation was obtained followed by five EKGs with QTc intervals no greater than 427 ms. Quetiapine was gradually increased to 800 mg daily in divided doses and fluphenazine 2.5 mg at bedtime was added. Citalopram 40 mg daily was continued. QTc interval was 411 ms at discharge. Two months after hospital discharge, the QTc interval was 433 ms and 3 months later a single QTc interval measurement was 455 ms with others in temporal proximity measuring less than 400 ms. Serial chemistries including serum electrolytes had been normal in the past.<br>The authors concluded that psychiatrists should always perform manual measurements of the QTc interval; psychiatrists should be alert to all potential adverse cardiac effects of antipsychotic drugs; and other risk factors besides psychotropic drug administration should be considered when adverse cardiac events occur |
| Case 5, 2004<br>[Kurth and Maguire, 2004]<br>'Pediatric case report of quetiapine overdose and QTc prolongation' | A 14-year-old boy overdosed on 1.9 g of quetiapine in a suicide attempt. Previous EKGs showed QTc intervals of less than 420 m. Half an hour to an hour after overdose, the QTc interval was 444 ms (measured). Forty minutes later, the QTc interval was 500 ms (measured) and he was transferred to the pediatric ICU. Chemistries including serum electrolytes were normal. Six hours later, the QTc interval had returned to normal (436 ms) |

*(Continued)*

**Appendix A.** (Continued)

| Year and case report | **Comment** |
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| Case 6, 2005 [Vieweg *et al.* 2005] 'Torsade de pointes in a patient with complex medical and psychiatric conditions receiving low-dose quetiapine' | A 45-year-old woman with multiple medical problems taking low-dose quetiapine received albuterol in the ambulance en route to the hospital. The cardiac monitor showed 'ventricular fibrillation' followed by a generalized seizure. Countershock restored normal rhythm. In the ED, the initial EKG showed QTc interval prolongation of 548 ms. Three minutes later, the cardiac monitor showed classical *TdP* lasting less than 10 min. The post-*TdP* EKG was consistent with the long QT syndrome [Vincent, 1999]. Serum magnesium and calcium concentrations were low. Interview revealed that she was taking escitalopram 20 mg and quetiapine 100 mg daily. Diagnoses included ventricular fibrillation, QTc interval prolongation, anemia, hypertension, depression, and ethanol abuse.<br>The authors concluded that quetiapine administration, when accompanied by risk factors, may contribute to cardiac arrhythmias including *TdP* |
| Case 7, 2006 [Strachan and Benoff, 2006] 'Mental status change, myoclonus, electrocardiographic changes, and acute respiratory distress syndrome induced by quetiapine overdose' | A 41-year-old man presented to the ED with seizure-like activity. Two days earlier, he was discharged from the hospital following treatment for depression with suicidal ideation and received quetiapine 25 mg twice daily, valproic acid 250 mg twice daily, gabapentin 300 mg three times daily, desipramine, paroxetine 20 mg daily, hydroxyzine 10 mg twice daily, and atorvastatin 10 mg daily.<br>On the day of current hospitalization, he overdosed with quetiapine (4.5 g) in a suicide attempt. His parents noted seizure-like activity and called the emergency services when intravenous lorazepam was administered without effect. In the ED, his Glasgow Coma Scale score was 8/15, frequent myoclonic jerks and startle myoclonus were noted, and the EKG showed a heart rate of 98 bpm, a widened QRS duration (140 ms), and QTc interval prolongation (684 ms). An acute respiratory distress syndrome complicated by gram-negative septicemia led to a 5-week stay on the Medical Service followed by a transfer to the Psychiatry Service. Even though desipramine had been prescribed and his serum tested positive for tricyclic antidepressants, the large dose of quetiapine likely explained the initial QTc interval prolongation. *TdP* was not reported. |
| Case 8, 2008 [Bodmer *et al.* 2008] 'Pharmacokinetics and pharmacodynamics of quetiapine in a patient with a massive overdose' | A 34-year-old woman was seen in the ED because of quetiapine overdose in a suicide attempt. Next to the patient, an empty bottle previously containing 100 quetiapine 300 mg tablets (totaling 30 g) was found.<br>Hospital admission Glasgow Coma Scale score was 7/15 rapidly declining to 5/15. Serum electrolytes were normal. EKG showed a heart rate of 143 bpm, QT interval 400 ms, and QTc interval 620 ms (Bazett). The Bazett formula is highly inaccurate at this heart rate [Indik *et al.* 2006]. Despite a stormy hospital course, 11 h after presentation QTc interval was normal (430 ms). *TdP* was not reported |
| Case 9, 2010 [Digby *et al.* 2010] 'Multifactorial QT interval prolongation' | **Second case in this paper**<br>A 58-year-old woman who chronically abused alcohol presented to an outlying ED complaining of weakness, nausea, diaphoresis, and malaise. Medical problems included heart failure, chronic obstructive lung disease, obstructive sleep apnea, and hypertension. Psychotropic medications included quetiapine (50 mg three times daily and 200 mg every night), citalopram (60 mg daily), clonazepam (1 mg three times daily), acamprosate (333 mg three times daily), and mirtazapine (30 mg every night). She also took diuretics and other drugs for her medical problems.<br>Initial laboratory testing revealed hypokalemia (2.5 mmol/liter) and borderline hypomagnesemia (0.75 mmol/liter, 1.8 mg/dl). EKG showed QTc interval of 720 ms and episodic *TdP*. She was transferred to a tertiary care hospital requiring numerous countershocks to manage three episodes of ventricular fibrillation en route. On arrival, she was treated with intravenous magnesium, metoprolol, and a temporary transvenous pacemaker to increase the heart rate to 120 bpm. All medications associated with QTc interval prolongation were stopped. The QTc interval normalized, *TdP* did not recur, and follow-up QTc interval was 410 ms. |

*(Continued)*

**Appendix A.** (Continued)

| Year and case report | **Comment** |
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| | The authors hypothesized that QTc interval prolongation was likely associated with citalopram and quetiapine administration. They described a paper by their group in which QTc interval prolongation was associated with overdose of escitalopram, morphine, oxycodone, zopiclone, and benzodiazepines [Baranchuk *et al.* 2008]. We believe it is far more likely that hypokalemia explained the QTc interval prolongation and recurrent *TdP*. Also, the authors apparently did not recognize that citalopram and escitalopram, although closely related, are not the same drugs. We have recently reviewed citalopram, QTc interval prolongation, and *TdP* [Vieweg *et al.* 2012] |
| Case 10, 2011 [Aghaienia *et al.* 2011] 'Probable quetiapine-mediated prolongation of the QT interval' | A 63-year-old woman with multiple medical problems including diabetes mellitus, hyperlipidemia, ataxia, and suspected tardive dyskinesia coupled with schizoaffective disorder was taking atorvastatin, estropipate, famotidine, lorazepam 1 mg daily, medroxyprogesterone, montelukast, omeprazole, paroxetine 40 mg daily, quetiapine extended release 800 mg daily, sitagliptin, trihexyphenidyl 7.5 mg daily, and vitamin D. Past history was consistent with ziprasidone-induced QTc interval prolongation.<br>She presented to the ED with disorganized behavior. Laboratory testing showed hyponatremia (130 mmol/liter) and hypokalemia (2.7 mmol/liter). Baseline EKG showed QTc interval prolongation (525 ms). Paliperidone was substituted for quetiapine. Hypokalemia was corrected, QTc interval returned to normal, and organization and cognition improved.<br>After discharge, she resumed quetiapine. Confusion and mood instability returned 1 month later and she was rehospitalized. Paliperidone replaced quetiapine and she was discharged. We believe hypokalemia better explained QTc interval prolongation than quetiapine administration. QTc interval returned to normal once hypokalemia was corrected and QTc interval prolongation did not return when quetiapine was restarted |
| Case 11, 2011 [Digby *et al.* 2011] 'Acquired long QT interval: a case series of multifactorial QT prolongation' | A 67-year-old woman with coronary artery disease, atrial fibrillation, prosthetic tricuspid valve replacement, epicardial pacemaker (DDD), chronic obstructive pulmonary disease, right leg cellulitis, alcohol abuse, and depression presented to a peripheral hospital with delirium and what was thought to be seizure-like episodes. Her psychiatric medications included escitalopram 20 mg daily and quetiapine 50 mg four times a day. In the ED, she was found to be in PVT and was treated with magnesium sulfate and defibrillation. Her initial QTc interval was 610 ms. She was later treated with an amiodarone infusion. Hypokalemia (2.7 mmol/liter) and hypomagnesaemia (0.61 mmol/liter) were corrected and psychiatric medications were held. Her discharge QTc interval was 551 ms |
| Case 12, 2011 [Digby *et al.* 2011] 'Acquired long QT interval: a case series of multifactorial QT prolongation' | A 77-year-old woman with a history of hypertension, aortic stenosis, and mitral stenosis presented to the hospital with a 2-week history of weakness, lightheadedness, and palpitations. In the ED, she was bradycardic (32 bpm) with second degree heart block alternating with third degree heart block. Her initial QTc interval was 529 ms. While in the ED, she experienced a self-limiting episode of *TdP*. Her medications included citalopram 60 mg daily, amitriptyline 40 mg daily, quetiapine 25 mg daily, furosemide 40 mg daily, diltiazem 120 mg daily, and metoprolol 50 mg twice daily. Electrolyte abnormalities on presentation included hypokalemia (3.4 mmol/liter) and hypomagnesaemia (0.71 mmol/liter) and they were corrected. She underwent pacemaker insertion. She was assessed for possible surgical repair of her valvular heart disease. Preoperative coronary arteriography was normal; however, she was too frail to undergo surgery. She developed congestive heart failure, pneumonia, and died |

ED, emergency department; EKG, electrocardiogram; ICU, intensive care unit; PVT, polymorphic ventricular tachycardia; *TdP, torsade de pointes*.