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Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram

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Summary

Background: Although QT prolongation is associated with increased risk of torsade de pointes (TdP), the precise relationship is not well defined.

Aim: To evaluate the performance of a QT nomogram in assessing the risk of TdP from QT–RR combinations.

Design: Systematic review.

Methods: We systematically searched MEDLINE/EMBASE for cases of drug-induced TdP. Controls were patients taking non-cardiotoxic drugs in overdose. Inclusion criteria were definite TdP, normal ECG before or after the event, association with a drug/toxin and QT–RR measurements available. The upper bound of a QT–RR cloud diagram developed from human preclinical studies was converted into a QT nomogram [QT vs. heart rate (HR)]. QT–HR combinations for TdP cases and controls were plotted with the QT nomogram, and curves corresponding to a QTc = 440 ms

and QTc = 500 ms for comparison (Bazett's correction).

Results: We identified 129 cases of TdP. TdP cases occurred at lower HR values with longer QT intervals, with most cases occurring at HR 30–90 bpm. Controls were more evenly distributed, with HR 40–160 bpm. The sensitivity and specificity of the QT nomogram were 96.9% (95%CI 93.9–99.9) and 98.7% (95%CI 96.8–100), respectively. For Bazett QTc = 440 ms, sensitivity and specificity were 98.5% (95%CI 96.3–100) and 66.7% (95%CI 58.6–74.7), respectively, whereas for Bazett QTc = 500 ms they were 93.8% (95%CI 89.6–98.0) and 97.2% (95%CI 94.3–100), respectively.

Discussion: The QT nomogram is a clinically relevant risk assessment tool that accurately predicts arrhythmogenic risk for drug-induced QT prolongation. Further prospective evaluation of the nomogram is needed.

Introduction

Torsades de pointes (TdP) is defined as a polymorphic ventricular tachycardia characterized by a 'twisting of the points' around the isoelectric line on the electrocardiogram (ECG), and is preceded by a long QT interval.¹ TdP is potentially fatal, due to the propensity for it to degenerate into ventricular fibrillation.

Although QT prolongation is clearly associated with an increased risk of TdP, there is no reliable criterion to identify the length of QT prolongation that is associated with a clinically significant increased risk of TdP.² This makes it difficult for clinicians to decide what QT interval constitutes sufficient risk of TdP to require intervention.

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Table 1 HR correction formulae

Name	Formula
Bazett's Correction	$QTc = \frac{QT}{RR^{0.5}}$
Fridericia's Correction	$QTc = \frac{QT}{RR^{0.33}}$
Framingham Correction	$QTc = QT + 0.156 \times (1 - RR)$

QT in ms and RR in s.

The difficulty in interpretation of QT interval alone lies in its partial dependence on the heart rate (HR); for example, lower values of HR are naturally associated with longer QT intervals. Based on the dependence of QT on HR, most advocate calculation of a corrected QT (QTc), in which the QT interval is corrected to a standard HR value of, say, 60 bpm. The nature of the correction, and interpretation of a 'cut-off' value of QTc that confers an at-risk setting, are still debated.²

There have been significant reported problems with the use of HR correction formulas that produce a corrected QT (QTc), including Bazett's formula, the most commonly used correction. Another correction is that of Fridericia's (Table 1). Both Bazett's and Fridericia's corrections for HR apply a population mean correction factor for all patients. However, there is now strong evidence for significant inter-individual variability in the HR correction for QT,²⁻⁴ implying that the best HR correction for QT should be estimated for each individual.^{5,6} Unfortunately this cannot be done in the clinical setting, as it requires a number of normal QT measurements at varying HR for each patient.⁶ To help circumvent this problem we decided to evaluate the 'cloud' diagram proposed by Fossa *et al.*⁷ The 'cloud' diagram provides a region of normal QT-RR pairs, where RR denotes the R-R interval on the ECG. Fossa *et al.* previously suggested that QT-RR pairs outside the 95% 'normal' range may be associated with an increased arrhythmogenic risk. This provides a different approach to the assessment of pro-arrhythmic risk in QT prolongation, which does not require the use of correction formulas or numerous previous ECGs required for individual HR correction. To make this more clinically applicable we developed a QT nomogram based on the Fossa diagram that used QT-HR pairs rather than QT-RR pairs.

The aim of this study was to evaluate the performance of the QT nomogram in assessing the risk of TdP, comparing QT-HR combinations for known cases of drug-induced TdP cases to those of a negative control group with normal QT-HR values.

Methods

This study was a comparison between QT intervals in definite cases of drug-induced TdP and normal QT intervals that arose in a study of a population of patients taking non-cardiotoxic drugs in overdose. Cases of drug-induced TdP were obtained from a systematic review of the literature. Negative controls were obtained from a previous study of patients taking non-cardiotoxic drugs in overdose. Ethics approval to use the data arising from the non-cardiotoxic drug overdose data was provided by the Hunter Area Research Ethics Committee.

For the cases, inclusion criteria were a reported human case of TdP with a normal ECG before or after the event, and a clear temporal relationship (within 24 h or four half-lives of the drug) between drug administration/dose escalation and the TdP episode. Exclusion criteria were: not clearly drug-induced QT prolongation (minimal temporal relationship found, other factors e.g. congenital long QT syndrome) and where no QT or RR values were given (or could not be computed from the ECG data provided).

We systematically reviewed the literature to identify cases of drug-induced TdP. PreMEDLINE, MEDLINE and EMBASE were searched up until April 2006, with the search string: (exp 'tachycardia', 'ventricular'/or 'torsades de pointes') AND (case\$ or drug\$).mp limited to Human. Titles and abstracts were then searched to identify cases based on the inclusion criteria. Full articles for all potential cases were obtained and reviewed by two investigators (AC and GKI).

Cases that met the inclusion criteria were extracted onto a clinical report form and entered into a purpose built Microsoft Access database for analysis. Information collected from each case included: age and sex of the patient, pre-existing medical illnesses including any with a known risk for TdP, e.g. electrolyte imbalance, family history of congenital long QT syndrome, acquired cardiac disease (ischaemic heart disease, cardiac failure, cardiomyopathy), comprehensive drug history including all drugs being taken by the patient therapeutically or in overdose, timing of the TdP episode in relation to drug administration, timing of all ECGs, ECG measurements including QT, RR, HR and QTc from the ECG. ECG measurements were taken as close to an episode of TdP as possible and after recovery. Where an ECG was available, measurements of QT and RR were read manually using a previously developed approach.⁸ ECG intervals were measured on a 12-lead ECG manually with a ruler by one author. The QT interval was measured from the beginning of the Q wave

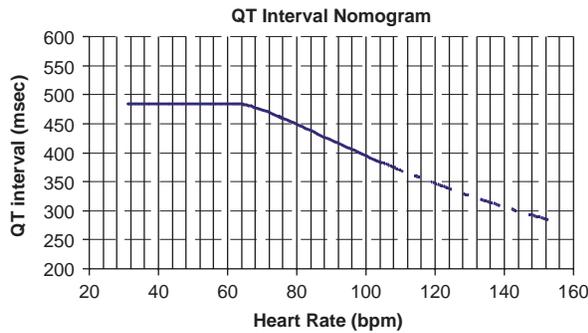


Figure 1. QT Interval Nomogram for determining 'at risk' QT–HR pairs from a single 12-lead ECG (modified from Figure 1 of reference 7). Use: The QT interval should be measured manually on a 12-lead ECG from the beginning of the Q wave until to the end of the T wave in multiple leads (i.e. six leads including limb and chest leads and median QT calculated). The QT interval is plotted on the nomogram against the heart rate recorded on the ECG. If the point is above the line then the QT–HR is regarded 'at risk'. A similar nomogram has been previously published without the extrapolation.¹⁰ The QT nomogram is included as supplemental electronic material (a Microsoft Excel worksheet) or can be obtained from the authors.

until the end of the T wave where the trace returned to baseline. The QT was measured in at least six leads, including chest and limb leads, and the median QT interval taken. The RR interval was measured from identical points in one complex to the next for at least six complexes in lead II, and the median taken. QT and RR measurements were derived from QTc and HR if these were the only information provided in the report.

Controls were taken from a previous study of ECGs taken in patients following an overdose of a drugs regarded as non-cardiotoxic: paracetamol, diazepam, oxazepam or temazepam.⁹ There were 318 patients, 215 females and 103 males with a median age of 34 years (interquartile range 23–45 years). The full dataset with QT and RR values was available to the authors.

The QT nomogram was developed based on a rearrangement of the Fossa 'cloud' diagram (from Figure 1 of reference 7). The Fossa 'cloud' diagram was scanned and data relating to the 'at risk' line were digitally extracted into a finite range of points and then converted into a QT vs. HR curve. A polynomial was then fitted through the points of the QT–HR data to provide a smoothed line (Figure 1). The polynomial was replaced by a horizontal straight line for HR values <60 bpm, as per the Fossa diagram. For values of HR >105 bpm (RR 570 ms), the equation was used to extrapolate the at-risk line, as the original diagram did not provide an at-risk region above these values.

In this region, the polynomial only minimally diverged from a straight line, with evidence of a weak convex relationship. The extrapolation provided a continuous framework of assessment of risk for HR values between 30 and 160 bpm. A similar nomogram without the extrapolation has been previously published with QT and HR.¹⁰

QT–HR pairs corresponding to each case and control were plotted on the QT nomogram. In addition, two curves corresponding to Bazett's correction factor at QTc values of 440 ms and 500 ms were also plotted. These values have been equated to medium and high risk values, respectively.¹¹

In addition to visual analysis, sensitivity and specificity analyses were performed.¹² Analyses were performed by tallying the number of cases above the predictive line and dividing this by the total number of cases (sensitivity) and by tallying the number of controls below the predicted line and dividing this by the total number of controls (specificity). Ninety-five percent confidence intervals (95% CIs) were calculated using a normal approximation.¹²

Results

The literature review identified 1838 articles. After initial screening, 329 articles were obtained in full. One hundred and thirty cases of drug-induced TdP met the inclusion criteria. Reasons for exclusion included: non-human study, no specific case data, i.e. review article or comment, insufficient evidence that a drug was implicated, insufficient ECG measurement data, i.e. only QTc available so the QT and HR could not be calculated, ECG not recorded within a reasonable time frame, or evidence of abnormal baseline ECG, e.g. presence of long QT syndrome.

Table 2 provides a list of the most common drugs found in the cases of drug-induced TdP. However, this study did not aim to establish causation for particular drugs, because in most cases patients were taking multiple medications. The median age of the patients was 53 years (interquartile range 36–68 years; range 10–95 years).

The QT–HR pairs of the TdP cases were plotted and compared to the QT nomogram based on Fossa, and the at-risk lines defined by Bazett's formula (Figure 2, **a** and **b**). The TdP cases occurred primarily at lower HR values with longer QT intervals, with most cases occurring at HR 30–90 bpm. The controls were more evenly distributed, with HR from 40 to 160 bpm. On visual inspection, it was clear that the QT–HR pairs for TdP

Table 2 List of drugs commonly associated with drug-induced TdP in this study

Drug	Only drug ingested	All cases with that drug
Pentamidine	6	10
Arsenic	4	4
Cocaine	3	3
Sauropus androgynus	3	3
Sotalol	3	7
Astemizole	2	2
Citalopram	2	2
Erythromycin	2	11
Acetylcholine	1	1
Amiodarone	1	11
Amisulpride	1	2
Bepredil	1	1
Cesium	1	1
Ciprofloxacin	1	4
Doxepin	1	1
Enalapril	1	5
Flecainide	1	4
Fluconazole	1	4
Fluoxetine	1	3
Haloperidol	1	6
Methadone	1	5
Parathion	1	1
Pimozide	1	1
Pipamperone	1	1
Quinidine	1	5
Terfenadine	1	7
Terodiline	1	6
Thioridazine	1	2
Voriconazole	1	1

cases fell predominantly above the QT nomogram at risk line, whereas the controls fell below. This distinction was less apparent when examining the extrapolated part of the QT nomogram.

The sensitivities and specificities of the QT nomogram, with and without the extrapolated portion (HR >104 bpm), Bazett's QTc=440 ms and Bazett's QTc=500 ms, are included in Table 3. There were five cases of TdP, all with therapeutic ingestion of drugs, which fell below the QT nomogram (Table 4). In three of the five cases the HR was in the region of the extrapolation. In the other two cases they were very close to the line.

Discussion

The QT nomogram was highly sensitive and specific for cases of drug-induced TdP, and appears to be a good risk assessment tool for QT prolongation. Although Bazett's formula had a better sensitivity,

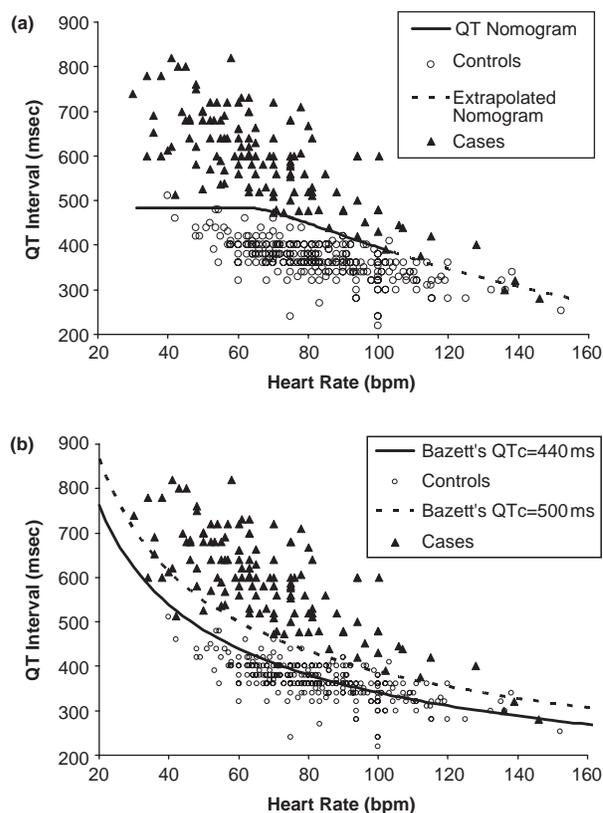


Figure 2. Plots of QT–HR pairs using **a** the QT nomogram and **b** against two 'at risk' lines defined by Bazett's QTc values.

at QTc=440 ms, and a similar specificity, at QTc=500 ms, in both scenarios the corollary statistic (specificity or sensitivity, respectively) performed worse. The QT nomogram gives an overall better prediction of TdP with high sensitivity and specificity. The study also demonstrates that most cases of TdP occur for HR between 30 and 90 bpm, and that tachycardia is seldom associated with TdP.

A previous study by Stratmann *et al.*¹³ reviewed TdP cases by examining baseline and pre-TdP values of QT and QTc. However, this study used QT and QTc without reference to heart rate.¹³ QTc has been suggested to be somewhat inaccurate in the prediction of TdP, due to the propensity of the most widely used correction factor (Bazett's) to overcorrect QT at fast heart rates (>70 bpm) and undercorrect QT interval at slow heart rates (<50 bpm).^{14,15} This was seen in our study, where Bazett's formula was conservative for tachycardia but underestimated risk for bradycardia. There are increasing reports of QTc prolongation in drug overdose, which may not reflect true cardiotoxicity, because tachycardia is a common finding in drug overdose. Quetiapine and bupropion have been attributed with cardiotoxicity, but studies have

Table 3 Sensitivity and specificity (95%CI) of the QT nomogram, compared to Bazett's QTc = 440 ms and QTc = 500 ms

	QT nomogram (with extrapolation)	QT nomogram (no extrapolation)*	Bazett's QTc = 440	Bazett's QTc = 500
Sensitivity	96.9% (93.9–99.9)	98.3% (96.1–100)	98.5% (96.4–100)	93.8% (89.6–98.0)
Specificity	98.7% (96.8–100)	99.3% (97.8–100)	66.7% (58.6–74.7)	97.2% (94.3–100)

*In this analysis, all cases with HR >104 bpm were excluded from analysis, so that only the original QT nomogram was used.

Table 4 Four cases that did not have QT prolongation based on the QT nomogram

Drug	Patient	Other factors	ECG parameters	Reference
Methadone	M31	None	HR 70, QT 472	18
Arsenic	M29	K ⁺ 3.3 mM	HR 146, QT 260	19
Arsenic	M43	None	HR 136, QT 300	19
Amiodarone/digoxin	F84	K ⁺ 3.4 mM	HR 102, QT 390	20

demonstrated that QTc prolongation with these two is likely due to overestimation of the QTc, due to tachycardia.^{16,17}

When examining the differences between the QT nomogram and the Bazett's correction factor, it can be noted that they differ significantly for HR below 60 bpm (bradycardic patients). It is this subset of patients who are more susceptible to developing TdP, with extreme bradycardia being a risk factor. This finding is in keeping with published reports, and is a serious inadequacy of the use of population mean correction factors.² Bazett's formula where QTc = 500 ms is similar to the QT nomogram for HR between 70 and 100 bpm, and this may be the reason for the relative success of this QT correction factor, although it is lacking in predictive accuracy below 60 bpm. Tachycardia seems to be particularly challenging to all three predictors. At faster HR (>100 bpm), the ability to read an exact value for QT is somewhat difficult by eye or for the digital ECG, thereby questioning the validity of some of the case points at these HR. However, examining Figure 2, there are relatively few TdP cases where the patient's HR is >110 bpm (7 cases). This may indicate a protective effect of tachycardia in the development of TdP. This is consistent with the recommendation to overdrive pace patients with QT prolongation to prevent TdP.

We repeated the analysis of the QT nomogram without the extrapolated portion of the curve. To do this, we censored cases with a HR >104 bpm and recalculated the sensitivity and specificity. This calculation (Table 3) demonstrates that the QT nomogram performs very well when used as

it was originally intended, and performs better than Bazett's formula when used on an intention-to-treat basis, including those patients with tachycardia.

Although our search for TdP cases was systematic, it was not exhaustive. It did not include searching databases of spontaneously reported adverse drug reactions or contacting pharmaceutical companies for any additional information. However, we assume that the cases located are representative of the wider body of events, and hence a more extensive search would be expected to provide for a stronger rather than different relationship, and a more conclusive endpoint.

Table 2 must be interpreted with caution, because this study did not aim to establish causation for particular drugs and the design was not appropriate for determining the frequency of TdP with each drug. The table merely provides some information on drugs commonly associated with TdP and the number of times they were involved in cases in this study.

There were four cases that would have not been classified as 'at risk' by the QT nomogram. Two of these cases had fast heart rates and were in the region of the extrapolation. The other two cases were almost on the QT nomogram, so there were no cases that were significantly below the unextrapolated line.

The QT nomogram attempts to overcome the limitations inherent in the use of population mean correction factors, such as that proposed by Bazett's formula. It should be noted that individual correction factors are preferred when conducting clinical studies,⁵ but these are not applicable to clinical

practice where they cannot be calculated easily. However, even in clinical studies where individual correction factors are estimated, the choice of a cut-off for the QTc value has not been established.⁸ Further work in this area is required.

It is well known that there is significant variation in the QT–HR with a single individual over time, including diurnal variation.² This variation produces a large range of QT–HR combinations in normal people. The advantage of the QT nomogram is that it defines a region of QT–HR combinations that are highly unlikely to occur in a normal individual even with such diurnal or other variation, and whose occurrence implies a risk of TdP. In borderline cases (near the nomogram line) repeat ECGs should be done to determine whether the patient is at risk of TdP.

In our retrospective case-controlled study, we chose a control group where patients have not ingested drugs that are known to be associated with TdP. This is a requirement of these types of studies. In doing so, we are making the reasonable assumption that any patient with a QT–HR combination above the QT nomogram is potentially at risk of developing TdP, and have then shown that the QT nomogram accurately separates these two groups.

For prospective cohort studies, it might be argued that a better control group would be patients who ingested drugs known to affect the QT interval but who did not develop TdP. However, because the relationship between QT prolongation and the development of TdP is still poorly understood and not quantified, using such a control group is problematic. This is the case even for prospective studies, since abnormal QT–HR values are a risk factor for which the hazard is continuous over the range of these values. For a patient ingesting a QT-prolonging drug with a QT–HR combination above the nomogram and not developing TdP, we do not believe the risk of developing TdP in this patient was truly zero, and hence these at-risk patients are essentially potential cases. Due to the extremely rare nature of TdP, a prospective study was not possible and for a retrospective case-controlled study, it is imperative that the controls are not matched to the cases for any factor for which the study attempts to define a relationship. In our case the factors of interest are at risk combinations of QT and HR. We thus chose controls where it was reasonable to assume the risk of TdP was close to zero, allowing the separation described above.

We elected to use overdose patients rather than the normal population as controls because it is commonly in the setting of drug overdose that

drug-induced QT prolongation occurs. A significant proportion of the cases of drug-induced TdP were due to drug overdose, so the control group was appropriate for these.

Conclusions

This study provides an initial evaluation for a clinically relevant risk assessment tool for drug-induced QT prolongation. This QT nomogram is based on a QT–RR cloud diagram developed from human preclinical studies by Fossa *et al.*, and accurately predicts arrhythmogenic risk. The nomogram is safe, with excellent sensitivity, and at the same time is specific enough to allow the assessment of many patients as ‘not at risk’ and therefore not require cardiac monitoring. The QT nomogram requires further investigation and evaluation.

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References

1. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. *Curr Opin Cardiol* 2007; **22**:39–43.
2. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug Saf* 2001; **24**:323–51.
3. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. *Heart* 2002; **87**:220–8.
4. Batchvarov VN, Ghuran A, Smetana P, Hnatkova K, Harries M, Dilaveris P, Camm AJ, Malik M. QT–RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. *Am J Physiol Heart Circ Physiol* 2002; **282**:H2356–63.
5. Piotrovsky V. Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. *AAPS J* 2005; **7**:E609–24.
6. Couderc JP, Xiaojuan X, Zareba W, Moss AJ. Assessment of the stability of the individual-based correction of QT interval for heart rate. *Ann Noninvasive Electrocardiol* 2005; **10**:25–34.
7. Fossa AA, Wisialowski T, Magnano A, Wolfgang E, Winslow R, Gorczyca W, Crimin K, Raunig DL. Dynamic beat-to-beat modeling of the QT–RR interval relationship: analysis of QT prolongation during alterations of autonomic state versus human ether a-go-go-related gene inhibition. *J Pharmacol Exp Ther* 2005; **312**:1–11.
8. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation

- following citalopram overdoses. *Br J Clin Pharmacol* 2006; **61**:177–90.
9. Isbister GK, Bowe SJ, Dawson A, Whyte IM. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; **42**:277–85.
 10. Isbister GK, Friberg LE, Duffull SB. Application of pharmacokinetic-pharmacodynamic modelling in management of QT abnormalities after citalopram overdose. *Intensive Care Med* 2006; **32**:1060–5.
 11. Fermini B, Fossa AA. The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat Rev Drug Discov* 2003; **2**:439–47.
 12. Daly LE, Bourke GJ. *Interpretation and uses of medical statistics*. Blackwell Science, 2000.
 13. Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. *Am Heart J* 1987; **113**:1470–82.
 14. Desai M, Li L, Desta Z, Malik M, Flockhart D. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2003; **55**:511–17.
 15. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol* 2004; **37** (Suppl.):81–90.
 16. Balit CR, Isbister GK, Hackett LP, Whyte IM. Quetiapine poisoning: A case series. *Ann Emerg Med* 2003; **42**:751–8.
 17. Isbister GK, Balit CR. Bupropion Overdose: QTc Prolongation and Its Clinical Significance. *Ann Pharmacother* 2003; **37**:999–1002.
 18. Gil M, Sala M, Anguera I, Chapinal O, Cervantes M, Guma JR, Segura F. QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol* 2003; **92**:995–7.
 19. Unnikrishnan D, Dutcher JP, Varshneya N, Lucariello R, Api M, Garl S, Wiernik PH, Chiamida S. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood* 2001; **97**:1514–16.
 20. Voigt L, Coromilas J, Saul BI, Kassotis J. Amiodarone-induced torsade de pointes during bladder irrigation: an unusual presentation—a case report. *Angiology* 2003; **54**:229–31.