Methods in Clinical Pharmacology Series

Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice

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There has been an increasing focus on drug induced QT prolongation including research on drug development and QT prolongation, following the removal of drugs due to torsades de pointes (TdP). Although this has improved our understanding of drug-induced QT prolongation there has been much less research aimed at helping clinicians assess risk in individual patients with drug induced QT prolongation. This review will focus on assessment of drug-induced QT prolongation in clinical practice using a simple risk assessment approach. Accurate measurement of the QT interval is best done manually, and not using the measurement of standard ECG machines. Correction for heart rate (HR) using correction formulae such as Bazett's is often inaccurate. These formulae underestimate and overestimate the duration of cardiac repolarization at low and high heart rates, respectively. Numerous cut-offs have been suggested as an indicator of an abnormal QT, but are problematic in clinical practice. An alternative approach is the QT nomogram which is a plot of QT *vs.* HR. The nomogram has an 'at risk' line and QT-HR pairs above this line have been shown in a systematic study to be associated with TdP and the line is more sensitive and specific than Bazett's QT_c of 440 ms or 500 ms. Plotting the QT-HR pair for patients on drugs suspected or known to cause QT prolongation allows assessment of the QT interval based on normal population QT variability. This risk assessment then allows the safer commencement of drugs therapeutically or management of drug induced effects in overdose.

Introduction

There has been an enormous amount of research on drug induced QT prolongation over the last few decades [1]. To date research has almost exclusively focused on drug development and the risk of particular drugs causing QT prolongation in populations of patients taking the drug therapeutically. The removal of a number of drugs from use in the last decade due to cases of torsades de pointes (TdP) [2, 3], has intensified mainly pharmaceutical industry research and prompted the development of guidelines for the *in vitro* and *in vivo* assessment of drug effects on the QT

interval [4]. This has improved our understanding of drug interactions and balancing the risk of QT prolongation *vs.* the benefit of the drug [5].

Unfortunately this research and such guidelines are of limited usefulness to the clinician dealing with individual patients who have suspected or confirmed drug induced QT prolongation. A good example is a physician treating patients with methadone [6]. Methadone is known to cause QT prolongation but TdP occurs only rarely and ceasing methadone is difficult because of its benefits and patient desire to continue [7, 8]. Another example is assessing patients who have taken an

overdose of a drug which may or may not cause QT prolongation. There is little information on how to develop a risk assessment in these patients, including (i) practical measurement of the QT interval in the clinical setting, (ii) heart rate correction of the QT interval and (iii) the threshold for an abnormal QT.

An additional problem with assessment of the QT interval for an individual patient for a particular drug is that in the majority of cases QT measurements are not available for the patient prior to commencing the drug or taking a drug overdose. In many cases the risk assessment has to be made from a single electrocardiogram (ECG) at the time the patient presents for medical attention.

There are previous reviews of the topic focusing on drug development [1] and consensus criteria for assessing the QT interval for new drugs [4]. This review will focus on the assessment of drug-induced effects on the QT interval in an individual patient following either therapeutic use or an overdose of a drug. The aim is to provide a practical approach to the risk assessment of the QT interval, including the measurement, heart rate correction and determining when the QT is abnormal.

Non-drug risk factors and the QT interval

The classic presentation of QT prolongation and TdP is with congenital long QT syndromes, including the more common autosomal dominant Romano-Ward syndrome and the less common Jervell and Lange-Neilsen syndrome associated with deafness [9]. Although there is now an increasing understanding of the underlying mechanisms of these congenital disorders, they are genetically and phenotypically heterogenous and associated with a variety of mutations in ion channel sub-units (potassium and sodium channels) and mutations in regulatory protein coding genes [9, 10]. Most of these may be associated with poor outcomes and have been reviewed in detail elsewhere [11, 12].

In addition to congenital long QT syndrome, there is increasing evidence that the QT interval is a heritable trait in healthy subjects [13, 14], and genetic variants may be important for determining people who may be at higher risk from drugs that cause QT prolongation. These genetic variants in total explain more of the QT variation (except heart rate) than any other factor including gender [14]. However, these patients are likely to have normal ECG morphology and normal or near normal QT off the drug making identification of this group difficult without exposing them to the drug.

There are numerous other physiological and acquired pathological factors that have been associated with QT prolongation and TdP. Female gender is associated with a longer QT interval of about 20 ms compared with men [15, 16]. Increasing age has been shown to be independently

associated with QT prolongation [17, 18]. There is also diurnal variation in the QT interval which makes it important to consider time of day in the assessment of the QT interval [15].

The most common pathological conditions associated with QT prolongation are electrolyte disturbance, including hypocalcaemia [19, 20], hypokalaemia [20–23] and hypomagnesaemia [22, 24]. In a study of amisulpride overdose hypokalaemia was significantly associated with patients with QT prolongation [25]. Hypoglycaemia has also been associated with a prolonged QT [26]. Other conditions that have possible associations with QT prolongation are myocardial ischaemia, cardiomyopathies, hypothyroidism, obesity and hypertension.

So far we have considered risk factors for QT prolongation. A more difficult issue is the risk factors for TdP, independent of risk factors for QT prolongation. QT prolongation is the most important risk factor for TdP and is also the marker for TdP. However, there is little information on what independently increases the risk of TdP for patients with a prolonged QT. For example, amisulpride overdose commonly causes QT prolongation but only a small proportion of cases with QT prolongation actually develop TdP [25].

Drugs that affect the QT interval

Numerous drugs have been associated with QT prolongation and over the last decade a number of drugs have been withdrawn from the market or restricted because of reports of QT prolongation and TdP [2, 5, 27, 28]. The list of drugs that cause QT prolongation differ between sources depending on how causality is assigned. Table 1 includes the more common drugs that have been associated with QT prolongation but is not exhaustive.

Almost all drugs that have been associated with QT prolongation block the rapid component of the delayed rectifier potassium channel (I_{KR}), which is coded by the human ether-a-go-go related gene (hERG) [29]. Blocking the I_{KR} channel results in prolonging the action potential which appears as lengthening of the QT on the ECG. This delayed ventricular repolarization leads to early after depolarizations, which can result in just focal activity or re-entrant pathways, and thence TdP [29]. However, it still remains unclear why some drugs that are potent blockers of I_{KR} and cause QT prolongation, rarely cause TdP such as amiodarone [23, 29].

It is important to remember that QT prolongation can result from multiple factors, either multiple drugs or a combination of drugs and non-drug factors [5]. Combinations of drugs may cause QT prolongation due to pharmacokinetic interactions such as ketoconazole inhibiting the metabolism of cisapride at the cytochrome P450 enzyme 3A4, or pharmacodynamic interactions when two drugs that cause QT prolongation are combined [5, 29]. The risk

Table 1

List of drugs with associated with a high risk of QT prolongation and TdP. A more comprehensive list of drugs associated with QT prolongation can be found at http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.cfm

Cardiac drugs	• Amiodarone • Sotalol • Disopyramide • Dofetilide • Procainamide • Quinidine
Antidepressants	• Selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine • Moclobemide • Tricyclic antidepressants* • Lithium
Antipsychotics	• Amisulpride • Chlorpromazine • Haloperidol • Ziprasidone • Thioridazine
Antihistamines	• Loratadine • Astemizole • Diphenhydramine
Antimicrobials	• Ciprofloxacin, moxifloxacin, sparfloxacin • Clarithromycin, erythromycin • Fluconazole, voriconazole • Pentamidine
Other drugs	• Chloroquine • Cisapride • Dolesatron • Methadone • Arsenic

*The QT prolongation with tricyclic antidepressants is usually from QRS widening without actual lengthening of the JT interval (QT interval minus the QRS duration).

assessment can be quite difficult for some drugs such as erythromycin [30]. The intravenous erythromycin formulation has been associated with QT prolongation, where as there is little evidence to support oral erythromycin by itself causing TdP [30]. However, the combination of oral erythromycin and cisapride is known to cause TdP because of erythromycin inhibiting the metabolism of cisapride, again at cytochrome P450 3A4 [5].
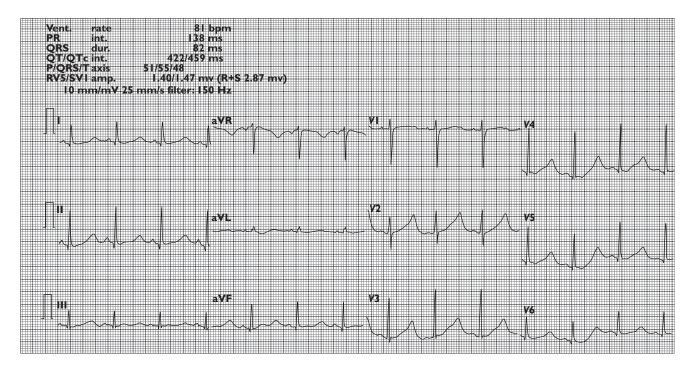
Measurement of the QT interval

There are numerous manual and automated approaches to measuring the QT interval. Important considerations are the method used to determine the end of the T wave, which lead is used, whether multiple leads are used, if multiple leads are measured is the median, maximum or mean (average) QT taken and whether a manual or automated measurement is used.

A major problem with measurement of the QT interval is defining the end of the T wave [1, 31, 32]. Morphological abnormalities in the T wave (e.g. biphasic T waves) and

distinguishing the T wave from the U wave may make determining the end of the T wave more difficult [1]. At least three methods are recognized for manual and automated measurement of the QT [31, 33, 34]. The simplest method is the visual method that identifies the point where the T wave returns to baseline (isoelectric line) [34]. The differential threshold method defines the end of the T wave as the point where the differential waveform of the T wave returns to the level of the background noise and is closest to the visual method [33]. The tangent method defines the end of the T wave as the intersection of the tangent of the steepest slope of the downward part of the T wave and the baseline or isoelectric line [31]. Although the tangent method has been shown to have less inter-reader variability, it gives a shorter measurement of the QT compared with the other methods and may be more inaccurate with unusual T wave morphology [33].

In many cases the QT is measured in only a single lead on the ECG. Lead II is most commonly used because it is more likely to have the longest QT interval. However, it only has the longest QT about 60% of the time [1]. Other leads have been suggested because they are more likely to have measureable QT intervals. A recent study showed that lead III, V1, aVF and aVL were more likely to have non-measureable QT intervals, compared with lead I and leads V3 to V6 [33], which was consistent with the choice of six leads in a study of manual QT measurements [34]. However, reliance on a single lead can be problematic if the tracing is unreadable in that lead [1]. A better approach is to measure more than one lead and take the median measurement [1, 34]. The median is more robust compared with the mean because an inaccurate measurement in one lead may cause a significant error in the mean. Another problem is the use of a single beat to measure the QT in each lead. More accurate approaches or algorithms will average 3 to 5 beats in each ECG lead which removes beat to beat variation and reduces artefact and noise.

Therefore to get an accurate measure of the QT interval, several beats in each lead should be averaged and then a median taken of six or more leads. This can either be done manually or automatically. A manual approach has the advantage of more accurately determining the end of the QT but is more time consuming because of the large number of QT intervals that need to be measured in each ECG. Automatic approaches allow the rapid measurement of large numbers of QT intervals but even the best algorithms may be inaccurate in determining the end of the QT interval [35].

Arguably the most accurate way to measure the QT interval is to use high-resolution digital 12-lead ECGs extracted from continuous 12-lead Holter recordings. A computer algorithm is then used to estimate the length of the QT from the digital 12-lead data. To increase the accuracy the digitized 12-lead ECG is displayed on-screen in a magnified view where the six limb leads and six chest leads are separately overlapped. On-screen callipers can

Figure 1

Standard 12-lead ECG of a valproate overdose showing QT prolongation of 560 ms by manual measurement but the automatic measurement is 422 ms

then be adjusted by a manual operator to confirm the automatic QT measurement and correct it if required. The equipment and technology is unlikely to be available outside of pharmaceutical development, although it has been used in a limited number of clinical studies and case reports [36–38].

Unfortunately in the clinical setting, currently the commonest way to measure the QT interval is to use the automatic measurement of the QT done by a standard 12-lead ECG machine. Although this is simple and used almost universally, it is unreliable, particularly for patients with a prolonged QT [1, 39]. This has been shown in a case of ziprasidone overdose where the automatically measured QT on the standard bedside ECG machine did not identify a prolonged QT, compared with both the automated 12-lead Holter measurement and manual measurement, which found a prolonged QT interval [36]. Another example of an inaccurate measure of the QT interval in a massive valproate overdose is shown in Figure 1 where the automatic measurement has an error of about 140 ms.

A better alternative in the clinical setting is using a manual measurement where more than one lead on the 12-lead ECG is measured and then the median QT interval is used. In this approach the QT interval is measured in one complex in each of six leads. The end of the T wave is determined visually as the point where it returns to baseline, the visual method [33]. This manual approach is a compromise between the time consuming measurement of multiple complexes in all 12 leads, and taking the poten-

tially inaccurate automatic measurement. The approach usually takes only 1 to 2 min with some practice. This is a small sacrifice for increasing the accuracy in the most important investigation for drug-induced QT prolongation. Such an approach has been suggested and evaluated in a recent study [34]. This method is summarized in Table 2.

Heart rate correction of the QT interval

The single most important parameter that affects the QT interval is the heart rate. This has been recognized for a long time with the initial development of Bazett's formula for heart rate correction [40] and subsequent changes to improve it [1]. However, the application of such heart rate correction formulae, including Bazett's, Fridericia, Hodges and Framingham, is problematic and does not completely remove the dependence of the QT on the heart rate and therefore does not allow comparisons of QT for different heart rates [41, 42]. This is most problematic with Bazett's formula which will over-correct and under-correct outside a narrow physiological range of heart rates [1, 41–44]. Unfortunately Bazett's formula is the most commonly used in clinical practice, despite warnings as early as the 1960's by Simonson [42] and numerous studies since that time [43, 45].

Table 2

A simple manual method for the measurement of the QT interval on the standard 12-lead electrocardiogram (ECG)

1 Measurement: The QT interval is measured in each lead of the ECG using a clear measuring ruler or by counting the small squares on the ECG paper when the paper rate is 25 mm s^{-1}. The QT interval is measured from the beginning of the Q wave until the T wave returns to the baseline (isoelectric line).
2 ECG leads: The QT is measured in a total of six leads including: • Three limb leads: I, II and usually aVF or aVL. Lead III is often low voltage and difficult to measure and aVR is inverted. • Three chest leads: V2, V4 and V6 if possible, although V3 and V5 may be used if there is a poor tracing in these leads. V1 is difficult to measure.
3 Median QT: The median of the six individual leads is then calculated.
4 Heart rate: The heart rate can be taken from the ECG machine's automated readout and is an average measure of the RR interval for the 12-lead ECG.
5 Absolute QT interval: Only the absolute QT interval is used and not the QT$_c$ or any correction of the QT interval.
6 QT nomogram: The QT is plotted against the heart rate on the QT nomogram (Figure 2). If the QT-heart rate pair is above the line on the nomogram it is abnormal and there is an increased risk of TdP.

Davey provides reasons for why Bazett's and formulae fail to correct the QT interval [41]. The first reason is that the formulae do not remove the dependence of the QT on the heart rate, which is worst in the case of Bazett's formula which over-corrects for fast heart rate indicated by the positive correlation between heart rate and the corrected QT interval (QT$_c$) [46]. This has been confirmed for Bazett's correction in a number of studies [47], including studies of drugs in overdose that cause tachycardia and artificially prolong the QT$_c$ [48–50]. This is a particular problem for quetiapine, a common drug taken in overdose which has been implicated as a drug causing TdP based only on cases of QT$_c$ prolongation, but no reports of TdP [51, 52]. Similarly venlafaxine overdose has been suggested to cause QT prolongation [53], but this was not confirmed when tachycardia was considered independently [49]. Fridericia and Hodges formulae are better but will still over-correct for fast heart rate.

The second reason that universal heart rate correction formulae have failed is that they correct for heart rate at the population level [54, 55]. The formulae assume that the relationship between QT and heart rate is fixed for different individuals [41]. Numerous studies have demonstrated that the QT/heart rate relationship is stable within an individual but varies significantly between individuals [54, 55]. Therefore, accurate heart rate correction of the QT interval can only occur if the relationship between heart rate and QT is known at the individual level. Such individual heart rate correction is possible in clinical research studies [54] and has been done in a number of population pharmacokinetic–pharmacodynamic studies of drugs in overdose that affect the QT interval, such as citalopram [56, 57].

Individual heart rate correction requires good baseline ECG data off the drug for establishing the QT/heart rate relationship and then multiple QT measurements on the drug. This is not possible in clinical practice because the patient usually presents for medical care when they are taking the medication or have taken an overdose and baseline ECGs are not available.

A third alternative to using either population heart rate correction or individual heart rate correction is to not correct the QT interval and plot the QT interval against the heart rate. This is the approach taken with the QT nomogram and is discussed below.
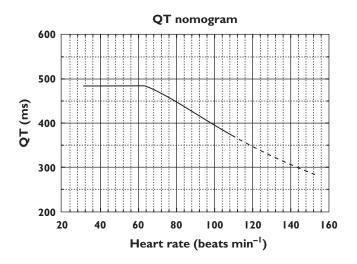
Risk assessment: When is the QT abnormal?

Numerous cut-offs have been suggested as the definition for an abnormal QT. One study showed that a QT$_c$ > 450 ms in men and QT$_c$ > 470 ms in women was associated with an increased risk of sudden death [58]. Another study of healthy volunteers found that the 95% confidence limit of the average 24 h QT$_c$ interval using Holter measurements was 450 ms overall, but 440 ms in men and 460 ms in women [15]. An absolute QT or QT$_c$ greater than 500 ms is often regarded as a significant risk of TdP [5, 59, 60].

The numerous different cut-offs used for an abnormal QT interval, and whether the QT$_c$ or absolute QT should be used makes it difficult for clinicians to determine if the QT interval is abnormal in any particular individual. An approach is required that gives a relatively sensitive and specific cut-off that can be applied at a population level that takes into account individual variation and includes heart rate correction.

The QT nomogram

To attempt to circumvent the problems with heart rate correction and what QT$_c$ cut-off to use, the QT nomogram was developed. The QT nomogram is based on the 'cloud' diagram produced by Fossa *et al*. [61] which is a plot of QT *vs*. the RR interval for a population. QT-RR plots in individuals each form a unique cloud which shows the variability in the QT-heart rate relationship, usually over a 24 h period. Individual clouds can be then superimposed and the inter-individual differences form a population cloud [62]. Fossa

et al. suggested that any QT-RR pairs outside this population 'cloud', which is the 95% 'normal' range, are associated with an increased risk of arrhythmia [61]. To make the QT-RR 'cloud' more practical for clinical use, the QT nomogram was developed which plots QT *vs.* heart rate but retains the same normal and 'at risk' regions (Figure 2) [63]. The advantage of this two-dimensional plot is that it does not require correction formulae and can be potentially used for single individuals.

The QT nomogram has been evaluated in a systematic review of cases of drug-induced TdP. This study showed that QT-heart rate pairs above the nomogram line were associated with TdP and that the QT nomogram was more accurate than Bazett's QT_c of 440 or 500 ms [63]. The QT nomogram had a sensitivity of 97% and specificity of 99% compared with Bazett's formula with a sensitivity of 99% and specificity of 67% ($QT_c = 440$ ms) and a sensitivity of 94% and specificity of 97% ($QT_c = 500$ ms), respectively.

A subsequent study has independently demonstrated that the QT nomogram is better than QT_c criteria, with a lower false positive rate [64]. The QT nomogram has been used in numerous studies of overdose patients as a risk assessment tool for QT prolongation and TdP [25, 49, 51, 56, 57, 65, 66] and examples of QT-heart rate plots are shown in Figure 3.

Like criteria based on a QT_c cut-off, the QT nomogram only indicates the presence or absence of an abnormal QT-heart rate pair, and does not quantify the risk or probability of TdP occurring. A recent study of amisulpride overdoses showed that the magnitude of the QT interval, by any of the common measures, is associated with an
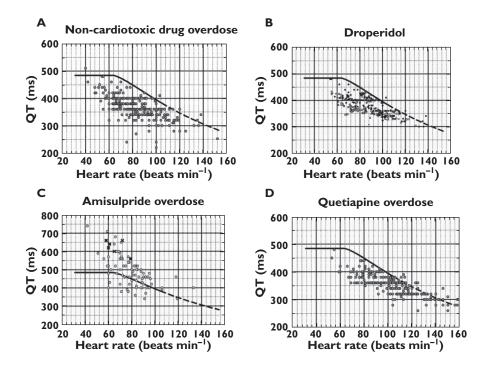
Figure 2

The QT nomogram developed by Chan *et al.* [63] The nomogram line separates HR,QT pairs above the line associated with an increased risk of torsades de pointes compared with those below the line

Figure 3

Plots of QT *vs.* heart rate on the QT nomogram for a control group of patients taking overdoses of drugs that do not affect the QT interval (paracetamol, diazepam, oxazepam and temazepam) (A), 10 patients given intramuscular droperidol for sedation where multiple ECGs were recorded over a period of 6 to 24 h using a 12-lead Holter recorder (B), 83 patients taking an amisulpride overdose including six who developed TdP (crosses) (C) and 260 patients taking a quetiapine overdose (D)
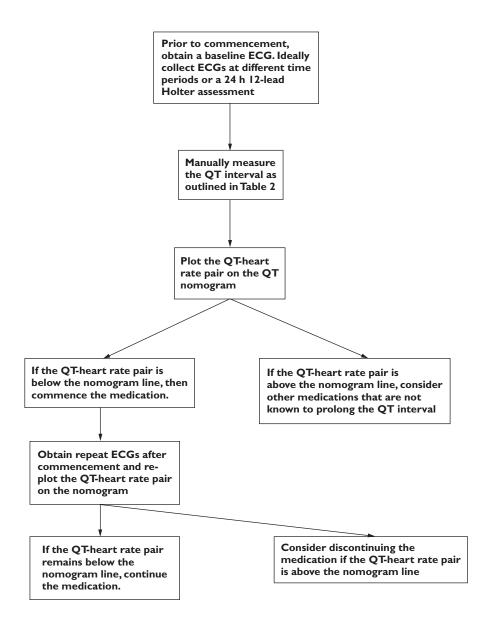
increasing risk of TdP [67]. Therefore, the greater the orthogonal distance above the QT nomogram line, the greater the risk of TdP for amisulpride. This suggests there is a relationship between the magnitude of the QT and the probability of TdP, but it is likely to differ for different drugs.

Assessing the risk of QT prolongation

Although QT prolongation can occur with the therapeutic use of drugs or drug interactions, it is more likely to occur in the setting of drug overdose. A difficult issue when assessing the risk of TdP is combining prior information on the drug that has been ingested with clinical information from the individual patient being assessed. For a limited number of drugs there is good evidence that the drug does or does not cause TdP. For example there are studies of amisulpride [25] and citalopram overdose [56] that clearly demonstrate a relationship between the drug and TdP, and in the case of citalopram a dose–effect relationship that has been used to develop clinical guidelines [68]. Conversely, a large study of quetiapine overdoses provides good evidence that quetiapine is highly unlikely to cause QT prolongation or TdP in overdose and patients do not require cardiac monitoring [51].

For other drugs there is limited information on the risk of TdP and the main issue for the treating clinician is at what cut-off value of the QT interval should patients be

Prior to commencement, obtain a baseline ECG. Ideally collect ECGs at different time periods or a 24 h 12-lead Holter assessment

Manually measure the QT interval as outlined in Table 2

Plot the QT-heart rate pair on the QT nomogram

If the QT-heart rate pair is below the nomogram line, then commence the medication.

If the QT-heart rate pair is above the nomogram line, consider other medications that are not known to prolong the QT interval

Obtain repeat ECGs after commencement and re-plot the QT-heart rate pair on the nomogram

If the QT-heart rate pair remains below the nomogram line, continue the medication.

Consider discontinuing the medication if the QT-heart rate pair is above the nomogram line

Figure 4
Recommended approach when commencing drugs that are known to prolong the QT interval

monitored. Measuring the QT interval manually using the method suggested in Table 2 and plotting the QT *vs.* the heart rate on the QT nomogram is a simple and practical way to assess the risk of QT prolongation in individual patients. This will assist in the decision to, or continue to, cardiac monitor the patient.

Prescribing drugs known to cause QT prolongation

A more difficult issue is deciding when the benefits of a drug that causes QT prolongation outweigh the risk of TdP. A good example of this is the prescription of methadone which is used widely as an opioid substitute and has significant benefits. Other examples are the use of antibiotics associated with a small risk of TdP or antidepressants and antipsychotics.

If it is decided that a drug known to cause QT prolongation and TdP is to be prescribed then it is important that there is appropriate baseline assessment and then monitoring while on the drug. A stepwise approach is recommended starting with a baseline ECG which is the minimum that should be done (Figure 4). However, a more accurate baseline assessment would be a number of ECGs at different times of the day or if available a Holter assessment of the QT [36]. This initial assessment is to determine if the patient has an 'off' drug abnormal QT which would preclude the use of any drug that prolongs the QT.

Once the patient is started on the medication it is important to follow up with ECGs on the drug to determine if there is evidence of QT prolongation. The approach in Table 2 can be used to determine if there is an abnormal QT. It is also essential to avoid other drugs that cause QT prolongation or other non-drug risk factors such as electrolyte abnormalities. Ultimately the use of QT prolonging drugs can be a difficult balance of benefit *vs.* risk for the treating clinicians.

Competing Interests

Both authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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