THERAPEUTIC ADVANCES in
Psychopharmacology

Original Research

Estimation of cardiac QTc intervals in people prescribed antipsychotics: a comparison of correction factors

Ther Adv Psychopharmacol

2022, Vol. 12: 1–12

DOI: 10.1177/20451253221104947

Teodora Andric, Karl Winckel, Timothy David Tanzer, Samantha Hollingworth, Lesley Smith, Katherine Isoardi, Olivier Tan and Dan Siskind

Abstract

Background: A prolonged electrocardiogram (ECG) QT interval is associated with cardiac events and increased mortality. Antipsychotics can prolong the QT interval. The QT interval requires correction (QTc) for heart rate using a formula or QT-nomogram. The QT and QTc can be calculated automatically by the ECG machine or manually; however, machine-measured QT(c) intervals may be inaccurate.

Objective: We aimed to investigate the mean QTc and proportion of prolonged QTc intervals in people taking antipsychotic medicines.

Methods: We conducted an observational retrospective chart review and data analysis of all consecutive patients taking antipsychotics, with an ECG record, admitted to the psychiatric unit of a large tertiary hospital in Brisbane, Australia, between 1 January 2017 and 30 January 2019. We investigated the mean QTc of people taking antipsychotics to determine differences using (a) machine *versus* manual QT interval measurement and (b) QTc correction formulae (Bazett, Fridericia, Framingham, Hodges and Rautaharju) and the QT-nomogram. We also determined the number of people with a prolonged QTc using different methods and compared rates of prolonged QTc with antipsychotic monotherapy and polypharmacy.

Results: Of 920 included people, the mean (±SD) machine-measured, Bazett-corrected QT interval (recorded from the ECG) was 435 ms (±27), significantly longer ($p < 0.001$) than the mean manually measured corrected QT intervals with Fridericia 394 ms (±24), Framingham 395 ms (±22), Hodges 398 ms (±22) and Rautaharju 400 ms (±24) formulae. There were significantly more people with a prolonged QTc using machine-measured QT and the Bazett formula (12.0%, 110/920) when compared with manually measured QT and the Fridericia formula (2.2%, 20/920) or QT-nomogram (0.7%, 6/920). Rates of QTc prolongation did not differ between people taking antipsychotic polypharmacy compared with monotherapy.

Conclusion: Machine-measured QTc using the Bazett formula overestimates the QTc interval length and number of people with a prolonged QTc, compared with other formulae and the QT-nomogram. We recommend manually measuring the QT and correcting with the Fridericia formula or QT-nomogram prior to modifying antipsychotic therapies.

Keywords: Antipsychotic, Bazett, ECG, QTc, Tachycardia

Received: 16 February 2022; revised manuscript accepted: 16 May 2022.

Correspondence to:
Teodora Andric
School of Pharmacy, The University of Queensland, 20 Cornwall Street, Woolloongabba, Brisbane, QLD 4102, Australia.

Pharmacy Department, Princess Alexandra Hospital, Brisbane, QLD, Australia
t.andric@uqconnect.edu.au

Karl Winckel
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Pharmacy Department, Princess Alexandra Hospital, Brisbane, QLD, Australia

Timothy David Tanzer
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Pharmacy Department, Princess Alexandra Hospital, Brisbane, QLD, Australia

Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Samantha Hollingworth
Olivier Tan
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Lesley Smith
Pharmacy Department, Princess Alexandra Hospital, Brisbane, QLD, Australia

Katherine Isoardi
Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Clinical Toxicology Unit, Princess Alexandra Hospital, Brisbane, QLD, Australia

Dan Siskind
Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Metro South Addiction and Mental Health Service, Brisbane, QLD, Australia

Background

People with severe mental illness (SMI) live with a high burden of excess morbidity and mortality.[1] Cardiovascular disease is the largest cause of 20-year reduction in lifespan among people with SMI.[2] This is likely due to sedentary lifestyle, as well as metabolic dysregulation and weight gain associated with SMI and antipsychotic medicines.[3–6] Antipsychotic medicines are a mainstay in treating people with schizophrenia and other psychotic disorders as they are highly effective in attenuating positive symptoms, preventing relapse and reducing the risk of death in both acute and long-term settings.[7–9] However, antipsychotic

medicines are associated with adverse events, including a prolonged QT interval.[9]

The QT interval represents the time taken for the ventricles to depolarise and repolarise. On an electrocardiogram (ECG), it is the interval from the beginning of the QRS complex to the end of the T wave.[10] A prolonged QT interval can lead to ventricular tachycardia (VT) and arrhythmias.[11] Polymorphic VT with a twisting of QRS complexes (around the isoelectric line) is known as Torsades de Pointes (TdP).[12] It is often self-limiting but in some cases it progresses to ventricular fibrillation and sudden cardiac death.[13]

Other classical features of TdP include a short-long-short R-R cycle which may disturb even repolarisation across the myocardial wall. There also tend to be longer (i.e. cycle length) first beats in VT than the subsequent arrhythmia complexes: a warm-up phenomenon.[13]

Antipsychotic medicines have been associated with sudden cardiac death, potentially due to an increased risk of TdP.[14] TdP may develop due to a delay in the net repolarising current *via* blocking of the Ik channel in cardiac myocytes (by the drug),[11] which can prolong the QT interval[13] and reactivate L-type calcium channels leading to early after depolarisations (EAD).[15] Since there are regional differences (of myocardial tissue) in action potential length, heterogeneous transmural repolarisation can create functional re-entrant pathways leading to the development of ventricular fibrillation and TdP, resulting in faintness, syncope and death.[11,13,16]

Derangements of serum potassium, calcium and magnesium and other electrolytes are known to contribute to arrhythmias.[17,18] Second-generation antipsychotics are associated with electrolyte disturbances such as hyponatraemia and hypokalaemia, although the mechanism remains unclear.[19–22] Along with (female) sex and age, other factors such as bradycardia, alcohol intake and illicit substance use are risk factors for a prolonged QT interval.[23,24]

There are two main limitations for accurately measuring the QT interval and assessing the risk of complications in clinical practice. First, many ECG machines routinely used in hospitals measure the distance from an ancillary line drawn from the peak of the T wave to an overestimated inflection point[25] which may be imprecise.[26,27] ECG machines can have trouble defining the end of T waves, especially when they have morphological variations (e.g. inversions, biphasic, flattened) or lie close to the U wave.[28–30] Since T and U wave fusion is subtle, it is the interpreter's responsibility to recognise the abnormality; often times this means selecting leads not showing U waves.[31] It has also been shown that automatic QT measurement by the (ECG) machine has high reproducibility and avoids variability inherent with measurement by different clinicians.[32] Confirming the machine-measured QT interval by manually measuring and calculating the median value of six leads is a more accurate way to measure the QT interval.[28,33,34] The American Heart Association recommends using the lead showing the longest QT interval.[31]

Second, the QT interval is dependent on the heart rate and must be corrected using a formula (QTc).[35] The Bazett formula was the first one developed (1920) and is the most commonly used correction formula.[36] However, the Bazett formula is known to overcorrect the QT interval at tachycardic heart rates (>100 bpm) and undercorrect at bradycardic heart rates (<60 bpm).[37–41] Many ECG machines use the Bazett formula for correction as the default.

Tachycardia is a common adverse effect of many antipsychotic medicines with α1-adrenergic and muscarinic receptor antagonism.[42] The widespread use of the Bazett formula has led to overestimating rates of QTc prolongation in people taking antipsychotic medicines and complicates the ability to assess the risk of cardiac events in people with antipsychotic-induced tachycardia. Global clinical guidelines suggest that the risk of TdP starts to increase with QTc values >470 ms for women and >440 ms for men, and the causative medicines should be ceased for QTc intervals >500 ms.[9] In addition, the Food and Drug Administration (FDA) has determined that 30 ms changes to the baseline QTc are clinically noteworthy, with increases of 60 ms potentially justify treatment discontinuation.[43] Several prospective antipsychotics were abandoned in the predevelopment phase because of prolonged QTc.[12,44] In clinical practice, effective antipsychotic medicines may be needlessly withdrawn due to falsely elevated QTc measurements.

Other formulae have been developed including the Fridericia, Framingham, Hodges and Rautaharju formulae (Supplementary Figure 1).[35] Fossa *et al.*[45] developed a QT-cloud diagram which consists of

QT-HR [heart rate (bpm)] plots of a population; any QT-HR pairs outside the 95% 'normal' range are associated with an increased risk of arrhythmia and TdP. A nomogram was subsequently developed to assist clinicians in assessing the risk of TdP in clinical settings and has a reported sensitivity of 96.9%.[37]

We aimed to determine any differences in the mean QTc interval measurements and the number of people estimated to have a prolonged QTc between (a) machine *versus* manual measurement methods; (b) the Bazett, Fridericia, Framingham, Hodges and Rautaharju formulae and the QT-nomogram; and (c) antipsychotic monotherapy *versus* polypharmacy.

Method

Study design

We conducted an observational retrospective audit of each unique person admitted to the mental health unit of a large metropolitan hospital in Brisbane, Australia, over 25 months (1 January 2017 to 31 January 2019). We included 920 people who received an antipsychotic medicine at any point in their admission, had an ECG performed and were not acutely intoxicated on illicit substances.

Protocol

We extracted data from the local electronic medical record (EMR) on regular antipsychotic and non-antipsychotic QT-prolonging medicines[46] (Supplementary Tables 1 and 2) for each person, including any 'when required' antipsychotic doses given 48 h prior to the ECG (i.e. as 24-h equivalent doses). People who did not have a dose of antipsychotic prior to the ECG recording (but did receive one later in their admission) were thus categorised into the 'no therapy' group. We calculated the olanzapine-equivalent dose for each antipsychotic using the defined daily dose (DDD) method.[47] The QT interval was extracted from ECG leads (see below) as were serum electrolyte concentrations (if they were available within two days from the ECG) of potassium, corrected calcium, and magnesium from the EMR. We excluded any person that was non-adherent to their prescribed antipsychotic medicine, those who were documented to be acutely intoxicated with illicit substances and people who did not have a practitioner-confirmed ECG.

ECG and heart rate measurement

The Philips PageWriter TC50 ECG machine report was used to tabulate the machine-measured QT and QTc (Bazett) interval, along with the heart rate. The QT interval estimation technique within PageWriter TC50 uses an ancillary line from the peak of the T wave to a point beyond the expected inflection point at the end of the T wave.[25] The machine had a resolution of 800 × 600 SVGA, 8000 Hz sampling rate and a standard paper speed of 25 mm/s.[48] We manually measured the QT interval in six ECG leads from a standard 12-lead electrode. The most well-defined leads were chosen from the chest (3) and limbs (3).[28,33,34] Leads showing U waves were avoided. To reduce inter-rater variability, one researcher (T.A.) measured all intervals and was trained by a clinical toxicologist (K.I.). A Bland–Altman plot testing for intra-rater variability suggested there was no proportional bias between two occasions of measurement ($p = 0.670$). We measured the QT interval from the beginning of the QRS complex to the end of the T wave using a magnifying electronic calliper function that was a feature of the EMR ECG recording. The end of the T wave was determined using the maximum slope technique.[49]

We calculated the QTc interval using the median QT interval (from six leads) and the Bazett, Fridericia, Framingham, Hodges and Rautaharju formulae. The median QT interval is recommended as it provides a more robust measurement compared to the mean.[28,33,34] The QT-HR pairs (using the median six-lead QT interval) were plotted on the QT-nomogram to determine whether the individual was at risk of TdP.

In clinical practice, any cases of QT prolongation should be assessed for QRS prolongation, as QT prolongation which is caused by QRS prolongation may have a different risk of TdP.

Statistical analysis

The mean population QTc intervals (ms) were calculated using the median six-lead QT interval (ms) that was individually corrected with the formulae (Bazett, Fridericia, Framingham, Hodges and Rautaharju). We determined whether there was a difference in the mean QTc interval calculated using the different formulae through sample paired *T*-tests using a significance level of $\alpha = 0.05$. For analyses where multiple testing was undertaken, we used a significance of $\alpha = 0.01$ to reduce the risk of a Type I error.

Table 1. Baseline characteristics of study population ($n = 920$).

Median age (IQR) (years)	39 (29–51)	
Sex	M: 545 (59.2%), F: 375 (40.8%)	
Heart rate (bpm)	Mean (±SD)	83 (±16)
	Range	32–149
Serum electrolyte levels (mmol/L)	Potassium	Normal: 587 (95.6%), Below range: 25 (4.1%), Above range: 2 (0.3%)
	Calcium albumin corrected	Normal: 612 (99.0%), Below range: 3 (0.5%), Above range: 3 (0.5%)
	Magnesium	Normal: 593 (96.0%), Below range: 25 (4.0%), Above range: 0 (0.0%)
Antipsychotic therapy	No antipsychotic therapy: 170 (18.5%)	
	Antipsychotic monotherapy: 509 (55.3%)	
	Antipsychotic polypharmacy: 241 (26.2%)	

IQR, interquartile range; SD, standard deviation.

Through chi-square and sensitivity analyses, we determined whether there was a difference in the number of people with a prolonged QTc using the correction formulae. We also compared treatment groups (no therapy *versus* any therapy and monotherapy *versus* polypharmacy). We used the Fridericia formula for dichotomous analyses as it is more accurate for patients with tachycardia.[40,50,51]

Three sensitivity analyses were conducted. In the first sensitivity analysis, we excluded people with below-range electrolyte (potassium, magnesium and corrected calcium) derangements as they can contribute to QTc prolongation (Supplementary Tables 3 and 4).[17,18] In the second sensitivity analysis, people who were taking non-antipsychotic QT-prolonging medicines (Supplementary Tables 5 and 6) were excluded. In the third sensitivity analysis, we compared no antipsychotic therapy groups to 'high-risk' monotherapy groups (i.e. people taking an antipsychotic medicine with a known risk of QT prolongation and TdP)[46] (Supplementary Table 7). We used SPSS version 27 (IBM) and GraphPad Prism 9 for statistical analyses.

Results

Of the 2025 unique persons identified, we excluded 1105 due to a non-confirmed ECG, non-adherence to medicines or acute illicit substance intoxication; 920 people were included.

The median age was 39 years [interquartile range (IQR): 29–51 years] and 59.2% were male (Table 1). The mean heart rate was 83 bpm [± standard deviation (SD): 16 bpm] [range: 32–149 bpm], with 5.3% of people with a heart rate <60 bpm (bradycardic) and 14.8% with a heart rate >100 bpm (tachycardic). Two in three people (66.2%) had all three serum electrolytes recorded within two days of their ECG. Most electrolyte levels recorded were normal (potassium: 95.6%, albumin corrected calcium: 99.0%, magnesium: 96.0%); the most common deviation were values below normal range.

Four in five people (81.5%) were taking at least one antipsychotic at the time of the ECG; the most commonly used were olanzapine (42.3%), quetiapine (16.1%) and risperidone (16.0%) (Supplementary Table 1). The median olanzapine-equivalent dose of antipsychotics was 10 mg (IQR: 2.5–20 mg) per day. There were 26.7% (246/920) of people taking medicines other than antipsychotics that have been reported to prolong the QTc. The most commonly prescribed non-antipsychotic QT-prolonging drugs were mirtazapine (7.3%), lithium (6.5%) and venlafaxine (4.9%) (Supplementary Table 2), all of which have limited evidence for risk of TdP.[46]

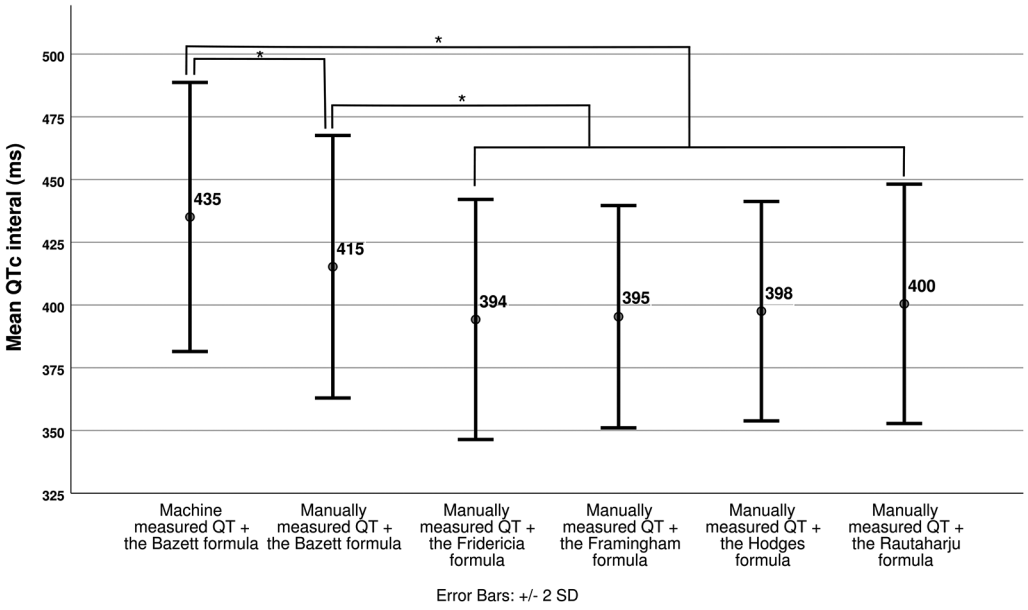

Figure 1. Mean corrected QT intervals (ms) obtained using various formulae. Machine-measured QT is the interval read from the ECG machine. Sample paired *t*-tests were conducted to calculate the *p* values.
*$p < 0.001$.

QTc calculation using formulae

The mean machine-measured QT interval recorded from the ECG and corrected using the Bazett formula was 435 ms (± SD 27, Figure 1). The mean manually measured corrected QT intervals were Bazett 415 ms (± SD 26); Fridericia 394 ms (± SD 24); Framingham 395 ms (± SD 22); Hodges 398 ms (± SD 22); and Rautaharju 400 ms (± SD 24, Figure 1). The mean QTc interval using the Bazett formula (either machine or manually measured) was significantly greater than all other formulae ($p < 0.001$); however, the manually measured QT interval was not statistically different at $\alpha = 0.01$ from the machine-measured QT interval when both were adjusted using the Bazett formula (Table 2).

The number of people with a prolonged QTc was significantly greater using machine-measured QT with the Bazett formula compared with manually measured QT with the Bazett formula (12.0% *versus* 8.8%, $p = 0.027$). Only 2.2% were identified with a prolonged QTc using the Fridericia formula; significantly less than with the machine-measured Bazett correction ($p < 0.001$). Less than one in a hundred (0.7%) were at risk of TdP using the QT-nomogram; the lowest proportion of all the calculation methods.

When we excluded people with below-range electrolyte derangements, there remained significantly fewer people identified as having a prolonged QTc with manually measured QT corrected with the Fridericia formula or the QT-nomogram than with machine-measured QT corrected with the Bazett formula (Supplementary Table 3). The same trend was seen when we excluded people taking non-antipsychotic QT-prolonging medicines (Supplementary Table 5).

We also compared no antipsychotic therapy to 'high-risk' antipsychotic monotherapy (i.e. monotherapy with antipsychotic medicines known to prolong the QT interval and increase TdP risk). There was no difference ($p = 0.361$) in the rate of QTc prolongation between the groups using an alternative calculation method (i.e. manually measured QT and the Fridericia formula) (Supplementary Table 7).

Of all the formulae, only the Bazett formula identified any people with severe QTc prolongation [i.e. QTc >500 ms (severe threshold)]. There were fivefold more people above the severe threshold using the machine-measured QT interval (2.0%, 18/920) than the manually measured QT interval (0.4%, 4/920, $p = 0.004$). This trend (i.e. $p < 0.05$) remained even after excluding people with below-range electrolyte levels or people taking non-antipsychotic QT-prolonging medicines (Supplementary Tables 3 and 5).

Table 2. Proportion of population identified as having a prolonged QTc using various calculation methods.

	Prolonged	Not prolonged	*p* value
Standard cut-off			
Machine-measured QT + the Bazett formula	110 (12.0%)	810 (88.0%)	
Manually measured QT + the Bazett formula	81 (8.8%)	839 (91.2%)	0.027*
Manually measured QT + the Fridericia formula	20 (2.2%)	900 (97.8%)	<0.001
Manually measured QT + the Rautaharju formula	27 (2.9%)	893 (97.1%)	<0.001
Manually measured QT + the QT-nomogram	6 (0.7%)	914 (99.3%)	<0.001
Severe cut-off			
Machine-measured QT + the Bazett formula	18 (2.0%)	902 (98.0%)	0.004
Manually measured QT + the Bazett formula	4 (0.4%)	916 (99.6%)	

Alternative calculation methods, using standard cut-offs [>440 ms (M), >470 ms (F)], were compared to Machine-measured QT + the Bazett formula. Machine-measured QT + the Bazett formula was also compared to manually measured QT + the Bazett formula using a severe cut-off [>500 ms]. Chi-square analysis was used to calculate *p* values.
*Fails to meet statistical significance with $\alpha = 0.01$.

The Bazett formula also appeared to underestimate rates of QTc prolongation in people with bradycardia. Two people who were below the prolonged QTc thresholds were identified as at risk of TdP using the QT-nomogram (Supplementary Figure 2).

Comparison of treatment regimes

There were no differences in the proportion of people with a prolonged QTc interval receiving either antipsychotic monotherapy or polypharmacy when measured using the various formulae (with machine and manual QT measurement) and the QT-nomogram (Table 3). There was also no difference in the proportion of people with a prolonged QTc receiving no therapy or any therapy when a manually measured QT interval and the Fridericia formula or QT-nomogram were used (Table 3). There was, however, a significantly higher ($p < 0.001$) proportion of people with a prolonged QTc when comparing no antipsychotic to any antipsychotic therapy when using a machine-measured QT interval and the Bazett formula. There was no difference in trend among treatment regimens when we excluded people with below-range electrolyte levels or people taking non-antipsychotic QT-prolonging medicines (Supplementary Tables 4 and 6).

Discussion

Machine-measured QT intervals and correction of the QT using the Bazett formula significantly overestimates the absolute QT interval length. This method may result in misclassification among people taking antipsychotic medicines who are at risk. We only detected severe prolongation (QTc >500 ms) using the Bazett formula. When using alternative calculation methods, there was no difference in the number of people with a prolonged QTc when we compared those taking antipsychotic monotherapy *versus* polypharmacy, those taking any antipsychotic therapy (monotherapy or polypharmacy) *versus* no antipsychotic therapy, nor those taking antipsychotic monotherapy with higher risk of prolonged QTc *versus* no antipsychotic therapy.

Of the 110 people identified as having prolonged QTc with machine-measured QT corrected with the Bazett formula, only 6 were considered at risk of TdP when QT was measured manually and plotted on the QT-nomogram. Furthermore, two people in bradycardic heart rate zones who were considered at risk of TdP using the QT-nomogram were not identified using the machine-measured [QT], Bazett-corrected QTc (Supplementary Figure 2).

The Bazett formula may overestimate QTc in people with tachycardia. This is less likely with

the other formulae. Antipsychotic-induced tachycardia is a common occurrence in people with SMI. In this population sample, the higher rates of prolonged QTc with the Bazett formula are likely due to overestimation secondary to antipsychotic-induced tachycardia. Concerningly, the Bazett formula may underestimate QTc in people with bradycardia, thus failing to identify people at higher risk of TdP.

Study strengths and limitations

To our knowledge, this is the first study to systematically explore both assessment of the QT interval and the impact of different formulae on identifying people with a prolonged QTc from a 'real world' clinical cohort of patients with SMI taking antipsychotic medicines. Only a few studies have explored QTc values in people taking antipsychotic and concomitant non-antipsychotic agents which may prolong the QT interval. These studies had smaller sample sizes (111–495 people)[5,11,52] and did not evaluate assessment methods.

We performed a sensitivity analysis excluding people taking non-antipsychotic QT-prolonging medicines which did not affect the significance of the results. The Bazett formula still identified significantly more people with a prolonged QTc compared to the Fridericia formula or QT-nomogram. Including people taking non-antipsychotic QT-prolonging medicines in our study portrays a more pragmatic, real-world estimate of the risk of QTc prolongation as there is common concomitant use of these agents as an adjunct to antipsychotic treatment.[9]

Some limitations are worth noting. Given the low incidence of QTc prolongation, there is the risk that analyses may have been insufficiently powered to disprove the null hypothesis. Second, some of our study population may not have reached steady-state plasma concentrations of antipsychotic at the time of the ECG; this might underestimate the risk of QT prolongation. Furthermore, the sample size prevented us from undertaking meaningful sub-analysis by individual antipsychotic when comparing antipsychotic polypharmacy and monotherapy. We were unable to ascertain whether people had electronic pacemakers which could widen the QT interval,[53,54] but we estimate the proportion of patients with pacemakers would be very low in our study population. Finally, this study did not consider the effect of non-psychotropic medicines (e.g. certain antibiotics, antihistamines) that can prolong the QTc interval.[46,55]

Table 3. Proportion of population from a treatment type identified as having a prolonged QTc using various calculation methods.

	Prolonged	Not prolonged	*p* value
Machine-measured QT + the Bazett formula			
No therapy	66 (38.8%)	104 (61.2%)	<0.001
Any therapy	44 (5.9%)	706 (94.1%)	
Monotherapy	33 (6.5%)	478 (93.5%)	0.314
Polypharmacy	11 (4.6%)	228 (95.4%)	
Manually measured QT + the Fridericia formula			
No therapy	4 (2.4%)	166 (97.6%)	0.775
Any therapy	16 (2.1%)	734 (97.9%)	
Monotherapy	10 (2.0%)	501 (98.0%)	0.625
Polypharmacy	6 (2.5%)	233 (97.5%)	
Manually measured QT + the Rautaharju formula			
No therapy	5 (2.9%)	165 (97.1%)	0.996
Any therapy	22 (2.9%)	728 (97.1%)	
Monotherapy	16 (3.1%)	493 (96.9%)	0.620
Polypharmacy	6 (2.5%)	235 (97.5%)	
Manually measured QT + the QT-nomogram			
No therapy	0 (0.0%)	170 (100.0%)	0.600
Any therapy	6 (0.8%)	744 (99.2%)	
Monotherapy	5 (1.0%)	504 (99.0%)	0.670
Polypharmacy	1 (0.4%)	240 (99.6%)	

Chi-square analysis was used to calculate *p* values.

Comparison to other literature

Our findings on the clinical limitations of current QTc interval measurement methods are consistent with other studies.[26,28–30,37–40] Patel *et al.*'s[51] study included a large (6723) multihospital tachycardic population from the University of Pennsylvania Health System without atrial fibrillation or flutter, who had an ECG recorded at an encounter with a practitioner but were not specifically receiving antipsychotic medicines. They

detected QTc prolongation in 39.0% of people using the Bazett formula, 6.2% using the Fridericia formula, 3.7% using the Framingham formula and 8.7% using the Hodges formula.[51] More than 2000 additional people with a prolonged QTc were identified using the Bazett formula compared with other formulae. Luo *et al.*'s[50] large (10,303) observational study also reported that the Bazett formula produced significantly higher QTc values than other formulae in a group with predominantly normal sinus rhythm, but, like for Patel *et al.*,[51] this study did not examine people taking antipsychotic medicines. It should be acknowledged that these studies used predominantly normal ECGs from structurally sound hearts. In reality, the risk of TdP is higher in non-normal populations (e.g. heart failure, bradycardia, left ventricular hypertrophy).[56,57]

So which formulae should be used instead of the Bazett formula? Many authors recommend correcting QT using the Hodges formula,[40,50,51] with Patel *et al.*'s[51] study suggesting it was the only formula shown to identify tachycardic individuals at higher risk of all-cause mortality.[51] Vandenberk *et al.*'s[58] work is the most extensive study ($n=49,737$) comparing performance of QT correction formulae and the association with mortality. It found that the Fridericia formula had the best regression slope in all heart rate ranges and had a superior prediction of mortality (*versus* the Bazett formula).[58] Therefore, we would advocate for the use of the Friderica formula. The QT-nomogram is highly sensitive and specific (96.9% and 98.7%, respectively) and has a superior prediction of TdP across all heart rate zones compared to the Bazett formula.[37]

We found no difference in the number of people with a prolonged QTc between those taking antipsychotic monotherapy *versus* polypharmacy; this contrasts with other studies.[59,60] Barbui *et al.*'s findings of an association between antipsychotic polypharmacy and QTc interval prolongation were based on a narrow range of (7) antipsychotics, 57.1% of which had evidence supporting that they prolong the QT interval (compared to 36.8% in our study).[46,60] However, it should be noted that this study assessed the risk of QTc prolongation using machine-measured QT and the Bazett formula. Furthermore, the mean antipsychotic dose was significantly higher for the polypharmacy group and the authors mention this as the main driving factor behind the small increase in QTc observed (7 ms). It is therefore likely that the increased incidence of QTc prolongation was simply due to increased rates of tachycardia. Although we found increased rates of prolonged QTc in people taking 'high-risk' antipsychotics when using machine-measured QT and the Bazzet formula, we did not see this when using manual QT measurement and an alternative formula.

Other authors have suggested there is no meaningful additional QTc prolongation when more than one QTc-prolonging medicine is used which is in keeping with our results.[61,62] Our study may have not been sufficiently large enough to detect a difference and is limited by the varied antipsychotics and doses used in the monotherapy and polypharmacy cohort.

Implications and recommendations

Our study suggests that machine-measured QT, corrected using the Bazett formula, significantly overestimates the QT interval length and may result in misclassification among people taking antipsychotic medicines. Consequently, people may have effective medicines inappropriately altered or ceased, increasing the chances of relapse and an unfavourable disease trajectory for those with SMI. For people with heart rates >60 bpm, a formula which more accurately accounts for drug-induced tachycardia such as the Fridericia formula is recommended. For people with heart rates <60 bpm, the QT-nomogram may be used. Future studies investigating the rates of QT prolongation should avoid the use of the Bazett formula.

In clinical scenarios, we suggest using a stepwise approach (Table 4) before any changes are made to antipsychotic treatment or management. We also urge medical supply companies who distribute ECG machines to provide options for correction formulae to minimise the clinical load of manual measurement.

Current dispensing and prescribing software often alerts and recommends against using combinations of antipsychotics. Conversely, our results support previous literature that suggests combinations of antipsychotics may not lead to clinically or statistically significant increases in the number of people with a prolonged QTc. We would still caution against prescribing antipsychotic polypharmacy for reasons such as tablet burden or, most notably, side effect burden, including additional metabolic or extrapyramidal adverse effects.[63]

Table 4. Approach to further examining machine calculated QTc.

ECG reading	Recommended action
>60 bpm	Manually measure the QT interval (in 6 ECG leads) and correct using the Fridericia formula
<60 bpm	Manually measure the QT interval (in 6 ECG leads) and plot the median on the QT-nomogram

ECG, electrocardiogram.

Conclusion

Machine measurement of the QT interval and correction with the Bazett formula overestimates the QTc when compared with other formulae and the QT-nomogram. There was no increased incidence of prolonged QTc in persons taking antipsychotic polypharmacy compared to monotherapy.

As clinical guidelines typically suggest the cessation of causative drugs,[9] accurate measurement of the QT interval prevents unnecessary withdrawal of effective therapy and risk of relapse and deterioration in mental state. Clinicians should manually measure the QT interval and use a method which accurately accounts for drug-induced heart rate changes such as the Fridericia formula or QT-nomogram prior to making any decisions to cease an antipsychotic.

Ethics approval and consent to participate

This study analysed deidentified, routinely collected administrative data which did not require patient consent according to local legislation. Ethical approval was obtained from the Metro South Human Research Ethics Committee (HREC/2020/QMS/69685)

Author contributions

Teodora Andric: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Karl Winckel: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

Timothy David Tanzer: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

Sam Hollingworth: Conceptualisation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

Lesley Smith: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

Katherine Isoardi: Conceptualisation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

Olivier Tan: Conceptualisation; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualisation; Writing – review & editing.

Dan Siskind: Conceptualisation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – review & editing.

ORCID iDs

Teodora Andric https://orcid.org/0000-0002-3025-6029

Timothy David Tanzer https://orcid.org/0000-0001-5924-3320

Dan Siskind https://orcid.org/0000-0002-2072-9216

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: DS is supported in part by an NHMRC EL2 Fellowship GNT1194635.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Supplemental material

Supplemental material for this article is available online.

References

1. Firth J, Siddiqi N, Koyanagi A, *et al.* The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019; 6: 675–712.
2. Lawrence D, Hancock KJ and Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* 2013; 346: f2539.
3. De Hert M, Detraux J, van Winkel R, *et al.* Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2012; 8: 114–126.
4. Reynolds GP and Kirk SL. Metabolic side effects of antipsychotic drug treatment – pharmacological mechanisms. *Pharmacol Ther* 2010; 125: 169–179.
5. Manchia M, Firinu G, Carpiniello B, *et al.* Clinicians' adherence to clinical practice guidelines for cardiac function monitoring during antipsychotic treatment: a retrospective report on 434 patients with severe mental illness. *BMC Psychiatry* 2017; 17: 121.
6. Carrà G, Bartoli F, Carretta D, *et al.* The prevalence of metabolic syndrome in people with severe mental illness: a mediation analysis. *Soc Psychiatry Psychiatr Epidemiol* 2014; 49: 1739–1746.
7. Kahn RS. On the continued benefit of antipsychotics after the first episode of schizophrenia. *Am J Psychiatry* 2018; 175: 712–713.
8. Leucht S. C.13.03 Translating the evidence on the clinical benefits of antipsychotics for routine practice. *Eur Neuropsychopharmacol* 2012; 22: S451.
9. Taylor D, Paton C and Kapur S. *The Maudsley prescribing guidelines in psychiatry*. 12th ed. West Sussex: Wiley Blackwell, 2015.
10. Goldberger AL, Goldberger ZD and Shvilkin A. *Clinical electrocardiography*. Philadelphia, PA: Elsevier, 2017.
11. Reilly JG, Ayis SA, Ferrier IN, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; 355: 1048–1052.
12. Schwartz PJ, Woosley RL and Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. *J Am Coll Cardiol* 2016; 67: 1639–1650.
13. Drew BJ, Ackerman MJ, Funk M, *et al.* Prevention of torsade de pointes in hospital settings. A scientific statement from the American Heart Association and the American College of Cardiology Foundation Endorsed by the American Association of Critical-Care Nurses and the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2010; 55: 934–947.
14. Ray WA, Chung CP, Murray KT, *et al.* Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360: 225–235.
15. Furutani K, Tsumoto K, Chen IS, *et al.* Facilitation of IKr current by some hERG channel blockers suppresses early afterdepolarizations. *J Gen Physiol* 2019; 151: 214–230.
16. Weiss JNMD, Garfinkel AP, Karagueuzian HSPF, *et al.* Early afterdepolarizations and cardiac arrhythmias. *Heart Rhythm* 2010; 7: 1891–1899.
17. Barr CS, Naas A, Freeman M, *et al.* QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994; 343: 327–329.
18. RuDusky BM. ECG abnormalities associated with hypocalcemia. *Chest* 2001; 119: 668–669.
19. Malik AR, Wolf PK and Ravasia S. Hypokalemia from risperidone and quetiapine overdose. *Can J Psychiatry* 2005; 50: 76–76.
20. Huang G, Fu Q and Xu J. Potential torsades de pointes triggered by hypokalemia related to olanzapine in a patient with implantable cardioverter-defibrillator. *J Clin Psychopharmacol* 2014; 34: 651–652.
21. Hoorn EJ and van der Poel MF. Hypokalemic hypertension related to clozapine: a case report. *J Clin Psychopharmacol* 2014; 34: 390–392.
22. Shah KB, Gupta SD, Rana DA, *et al.* Analysis of drug related electrolyte disturbances in emergency medicine department. *Int J Basic Clin Pharmacol* 2018; 7: 2005–2009.
23. Nosè M, Bighelli I, Castellazzi M, *et al.* Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study. *Epidemiol Psychiatr Sci* 2016; 25: 532–540.
24. Heemskerk CPM, Pereboom M, van Stralen K, *et al.* Risk factors for QTc interval prolongation. *Eur J Clin Pharmacol* 2018; 74: 183–191.

25. Zhou SH, Helfenbein ED, Lindauer JM, *et al.* Philips QT interval measurement algorithms for diagnostic, ambulatory, and patient monitoring ECG applications. *Ann Noninvasive Electrocardiol* 2009; 14(Suppl. 1): S3–S8.
26. Charbit B, Samain E, Merckx P, *et al.* QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. *Anesthesiology* 2006; 104: 255–260.
27. Savelieva I, Yi G, Guo X-h, *et al.* Agreement and reproducibility of automatic versus manual measurement of QT interval and QT dispersion. *Am J Cardiol* 1998; 81: 471–477.
28. Malik M and Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug Saf* 2001; 24: 323–351.
29. Lepeschkin E and Surawicz B. The measurement of the Q-T interval of the electrocardiogram. *Circulation* 1952; 6: 378–388.
30. Postema PG, De Jong JSSG, Van der Bilt IAC, *et al.* Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm* 2008; 5: 1015–1018.
31. Rautaharju PM, Surawicz B and Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram part IV: the ST segment, T and U waves, and the QT interval a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology the American College of Cardiology Foundation and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009; 53: 982–991.
32. Hnatkova K, Gang Y, Batchvarov VN, *et al.* Precision of QT interval measurement by advanced electrocardiographic equipment. *Pacing Clin Electrophysiol* 2006; 29: 1277–1284.
33. Isbister GK, Calver L, Van Gorp F, *et al.* Inter-rater reliability of manual QT measurement and prediction of abnormal QT, HR pairs. *Clin Toxicol* 2009; 47: 884–888.
34. Isbister GK and Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice: clinical assessment of drug-induced QT prolongation. *Br J Clin Pharmacol* 2013; 76: 48–57.
35. Vandenberk B, Vandael E, Robyns T, *et al.* Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc* 2016; 5: e003264.
36. Bazett HC. An analysis of the time-relations of electrocardiograms. *Ann Noninvasive Electrocardiol* 1997; 2: 177–194.
37. Chan A, Isbister GK, Kirkpatrick CM, *et al.* Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. *QJM* 2007; 100: 609–615.
38. Malik M, Färbom P, Batchvarov V, *et al.* Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. *Heart* 2002; 87: 220–228.
39. Kim DD, White RF, Barr AM, *et al.* Clozapine, elevated heart rate and QTc prolongation. *J Psychiatry Neurosci* 2018; 43: 71–72.
40. Chiladakis J, Kalogeropoulos A, Arvanitis P, *et al.* Preferred QT correction formula for the assessment of drug-induced QT interval prolongation. *J Cardiovasc Electrophysiol* 2010; 21: 905–913.
41. Andric T, Winckel K, Tanzer T, *et al.* Bazett's correction formula overestimates the corrected QT among patients with antipsychotic induced tachycardia. *Schizophr Res* 2021; 231: 22–23.
42. Michelsen JW and Meyer JM. Cardiovascular effects of antipsychotics. *Expert Rev Neurother* 2007; 7: 829–839.
43. Sager PT, Nebout T and Darpo B. ICH E14: a new regulatory guidance on the clinical evaluation of QT/QTc internal prolongation and proarrhythmic potential for non-antiarrhythmic drugs. *Ther Innov Regul Sci* 2005; 39: 387–394.
44. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; 350: 1013–1022.
45. Fossa AA, Wisialowski T, Magnano A, *et al.* 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.
46. AZCERT. CredibleMeds. *QTDrugs*. Arizona, 2012, https://crediblemeds.org/druglist
47. World Health Organization. *Guidelines for ATC classification and DDD assignment*. Geneva: World Health Organization, 1996.
48. Philips. PageWriter – TC50 Cardiograph. *Always in touch*, 2018, https://www.documents.philips.com/assets/20181011/4f1034155d134a0091cba976009a8218.pdf
49. Kasamaki Y, Ozawa Y, Ohta M, *et al.* Automated versus manual measurement of the QT interval and corrected QT interval. *Ann Noninvasive Electrocardiol* 2011; 16: 156–164.

50. Luo S, Michler K, Johnston P, *et al.* 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.

51. Patel PJ, Borovskiy Y, Killian A, *et al.* Optimal QT interval correction formula in sinus tachycardia for identifying cardiovascular and mortality risk: findings from the Penn Atrial Fibrillation Free study. *Heart Rhythm* 2016; 13: 527–535.

52. Warner JP, Barnes TR and Henry JA. Electrocardiographic changes in patients receiving neuroleptic medication. *Acta Psychiatr Scand* 1996; 93: 311–313.

53. Bibas L, Roy K, Sant'Anna R, *et al.* The effect of ventricular stimulation on the QT interval in patients with pacemakers. *Can J Cardiol* 2013; 29: S192.

54. Tang JKK, Bennett MT and Rabkin SW. Assessment of QT interval in ventricular paced rhythm: derivation of a novel formula. *J Electrocardiol* 2019; 57: 55–62.

55. Carrà G, Crocamo C, Bartoli F, *et al.* First-generation antipsychotics and QTc: any role for mediating variables? *Hum Psychopharmacol* 2016; 31: 313–318.

56. Heist EK and Ruskin JN. Drug-induced proarrhythmia and use of QTc-prolonging agents: clues for clinicians. *Heart Rhythm* 2005; 2(Suppl. 2): S1–S8.

57. Letsas KP, Efremidis M, Kounas SP, *et al.* Clinical characteristics of patients with drug-induced QT interval prolongation and torsade de pointes: identification of risk factors. *Clin Res Cardiol* 2008; 98: 208–212.

58. Vandenberk B, Vandael E, Robyns T, *et al.* QT correction across the heart rate spectrum, in atrial fibrillation and ventricular conduction defects. *Pacing Clin Electrophysiol* 2018; 41: 1101–1108.

59. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. *J Physiol* 2016; 594: 2459–2468.

60. Barbui C, Bighelli I, Carrà G, *et al.* Antipsychotic dose mediates the association between polypharmacy and corrected QT interval. *PLoS ONE* 2016; 11: e0148212.

61. Meid AD, Bighelli I, Mächler S, *et al.* Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *Ther Adv Psychopharmacol* 2017; 7: 251–264.

62. Niemeijer MN, van den Berg ME, Franco OH, *et al.* Drugs and ventricular repolarization in a general population: the Rotterdam study: drugs and ventricular repolarization. *Pharmacoepidemiol Drug Saf* 2015; 24: 1036–1041.

63. Barnes TRE and Paton C. Antipsychotic polypharmacy in schizophrenia: benefits and risks. *CNS Drugs* 2012; 25: 383–399.