

To the heart of ECG: a pocket guide for psychiatrists



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Foreword

For more than 50 years, antipsychotic agents have shown their great value in the treatment of psychotic conditions, and particularly schizophrenia. In recent times, a number of new antipsychotics with superior therapeutic profiles have also been developed.

It has become increasingly apparent, however, that all antipsychotics – including the newest drugs for the treatment of psychosis – have side effects, including an increased risk of metabolic syndrome and cardiovascular complications. There is also a risk of sudden cardiac death with some of these agents, which, although rare, has attracted growing attention and caused considerable anxiety to many relatives. These concerns, which are also associated with other prescribed psychopharmaceuticals, natural remedies and the use of polypharmacy, have clear implications for patients in terms of lifestyle and the potential for weight gain, inactivity or drug abuse.

It is therefore essential that patients with schizophrenia are closely monitored for adverse effects, including the metabolic syndrome and cardiovascular side effects. Many psychiatric wards already conduct systematic registration of patients for metabolic

syndrome and it is recommended that this is extended to include regular electrocardiogram (ECG) and blood pressure monitoring. Several antipsychotics affect blood pressure and prolong the QT interval, among them the recently launched and largely well-tolerated agent sertindole, for which regular ECG monitoring is now obligatory. In this regard, I would like to encourage physicians to ensure that cardiovascular monitoring becomes mandatory for all patients receiving antipsychotic drugs.

For most doctors, it is practically impossible to overview accurately the pharmacodynamic and pharmacokinetic properties and interactions of every prescribed drug in relation to the patient's potential for metabolic variations and use of non-prescribed drugs. This adds further weight to recommendations for systematic cardiovascular monitoring of all patients receiving antipsychotics. Issues such as this influence the image of psychiatry among the public at large and we must ensure that patients and their relatives are able to feel confident with us.

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Introduction

Schizophrenia is associated with a significant increase in the risk of mortality from both natural and unnatural causes.¹ One meta-analysis has shown that the risk of all-cause death in schizophrenia patients is 1.6 times higher than expected, while the risk of death from unnatural causes is 4.3 times higher and the risk of suicide is 9 times higher.²

Physicians have been aware of electrocardiographic (ECG) abnormalities and incidences of sudden cardiac death (SCD) in schizophrenia patients receiving antipsychotic medications since the 1960s when thioridazine was shown to prolong the QT interval.^{1,3,4} In general, ECG changes may be expected with almost all antipsychotic drugs and ECG monitoring is considered good clinical practice when prescribing these drugs.^{3,5,6} For the newer atypical agent sertindole, product labelling mandates ECG monitoring of the QT interval as a safety precaution.⁷

This booklet will describe the electrophysiology of the heart and the QT interval as a component of the ECG trace. The implications of a prolonged QT interval and factors that can exacerbate the risk of QT prolongation will then be outlined. Finally, the risks of QT prolongation associated with antipsychotic medications and methods for minimizing those risks will be presented.

Basics of ECG analysis

Basic electrophysiology of the heart^{3,8,9}

- The depolarization and repolarization of the myocardial cells of the heart during systole and diastole are evident as changes in voltage potential of 1–20 mV at the body surface
- At rest, the voltage difference between the inside and outside of the cell is -90 mv. The difference is due to the high intracellular K⁺ levels maintained by the sodium–potassium pump
- The depolarization of cardiac cells during systole occurs with a sudden increase in membrane permeability to Na⁺ such that the cells lose their negative resting voltage
- Cellular electrolyte balance is restored with repolarization during subsequent diastole

The ECG^{8,9}

The standard 12-lead ECG records the energy of the heart's electrical impulses from 12 directions during systole and diastole.

- Using the 12-lead ECG, specific regions of the heart can be assessed:
 - Six chest leads (V1–V6) record the activity of the heart in a horizontal plane, enabling its anterior, lateral and posterior aspects to be evaluated
 - Six limb leads (I, II, III, aVR, aVL, aVF) placed in a triangular formation enable analysis in a vertical plane from its inferior and lateral aspects
- On the ECG trace, a positive electrical impulse moving away from the lead is converted into a downward wave, while a positive impulse moving towards the lead is converted into an upward wave

Components of the ECG trace ^{8,9}

The ECG trace comprises a number of elements, including the P wave (represents atrial electrical activity), the QRS waves (ventricular electrical activity), and the T wave (ventricular repolarization) (Figure 1, Table 1).

- A range of abnormalities of heart rhythm can be detected by ECG assessment, including bradyarrhythmias (heart block, asystole) and tachyarrhythmias (supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation)

Figure 1. Schematic ECG trace¹

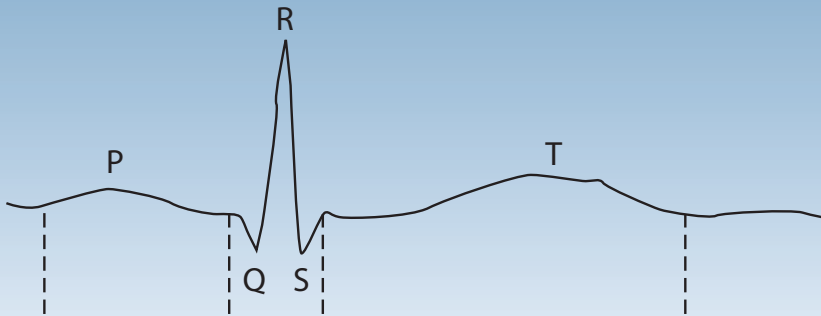


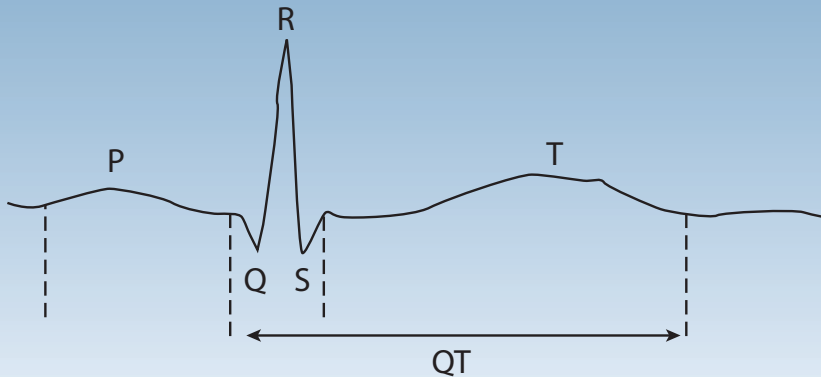
Table 1. Components of the ECG trace and how these may be used to identify abnormalities^{3,8}

Wave	Representation
P wave	<ul style="list-style-type: none"> • Low voltage signal of approximately 1 mV representing depolarization and contraction of the right and left atria • A clear P wave before the QRS complex represents sinus rhythm. P waves should normally be upright in leads I, II, aVF and V4–V6 • Absence of P waves may suggest atrial fibrillation, junctional rhythm or ventricular rhythm. P waves may be difficult to observe in ECGs with a high signal-to-noise ratio (e.g. tremor)
QRS complex	<ul style="list-style-type: none"> • Follows P wave and represents depolarization and contraction of the right and left ventricles • The QRS complex is the largest voltage deflection of approximately 10–20 mV but may vary in size depending on age, gender and presence / absence of obesity. The voltage amplitude may also give information about underlying cardiac disease • Duration of the QRS complex indicates the time for the ventricles to depolarize and may give information about conduction problems in the ventricles such as bundle branch block
QT interval	<ul style="list-style-type: none"> • Duration from beginning of QRS complex to end of T wave • Provides estimate of the time from earliest ventricular depolarization to the latest ventricular repolarization • Believed to reflect action potential duration in the underlying myocytes • Can vary considerably depending on techniques used for ECG measurement, intra-individual variability, certain conditions and use of some medications (see page 13)
T wave	<ul style="list-style-type: none"> • Represents ventricular repolarization • T waves should normally be upright in leads I, II and V3–V6 • Very tall T waves may represent ischaemia, acute infarction or severe hyperkalaemia

Implications of a prolonged QT interval

- The QT interval measures the time between the onset and end of electrical ventricular activity and is calculated on the ECG trace as the time from the beginning of the QRS complex to the end of the T wave (Figure 2) ^{1,3,8}

Figure 2. The QT interval measured from an ECG ¹



Factors that can prolong the QT interval^{1,3,10–13}

- The QT interval can be prolonged by a number of factors, including (but not limited to):
 - Heart rate (QT becomes longer as heart rate decreases)
 - Age
 - Gender (females have longer QT intervals than males; ~8–10 msec)
 - Electrolyte disturbances
 - Presence of U waves
 - Certain drugs
 - Conditions such as alcoholism, obesity, hypertension, cardiac ischaemia, diabetes, renal / hepatic failure and congenital long-QT syndrome
- Other factors that may affect the QT interval include:
 - ECG leads and methodology used
 - Circadian rhythm
 - Physical activity
 - Postural factors
 - Food intake
- Several correctional factors have been suggested to adjust for the effect of heart rate on the QT interval. None are ideal as they tend to overcorrect the QT interval when the heart rate is high and undercorrect when the heart rate is low. Bazett's formula ($QTcB = QT / RR^{0.5}$)¹⁴ and Fridericia's formula ($QTc = QT / RR^{0.33}$)¹⁵ have been most commonly used

Prolongation of the QT interval

- Prolongation of the QT interval is of clinical importance as it is thought to be associated with a risk of the ventricular arrhythmia known as Torsade de Pointes (TdP) or 'twisting of the points'. TdP can give rise to palpitations, presyncope or syncope and occasionally converts to ventricular fibrillation or SCD^{1,3,13,17}
- A QTc interval of >500 msec is associated with an increased risk of TdP.^{1,3,6,13,17–19} The globally recognized threshold levels for clinically noteworthy changes in the QT / QTc interval are presented to the right¹⁶
- On the ECG, TdP is characterized by rapid, irregular, sharp complexes that continuously change from an upright to an inverted position (Figure 3). Prior to and between spells of tachycardia, the ECG shows a prolonged QT interval
- It should be noted that QT prolongation alone is not predictive of the development of life-threatening arrhythmias and TdP.¹ In order to induce TdP, heterogeneity in the duration of the action potential across different cardiac cell types seems to be an important substrate. Likewise, a required trigger, such as an early after-depolarization (EAD) – a form of spontaneous depolarization that results in abnormal rhythmic activity – appears to be needed to facilitate TdP^{1,20,21}

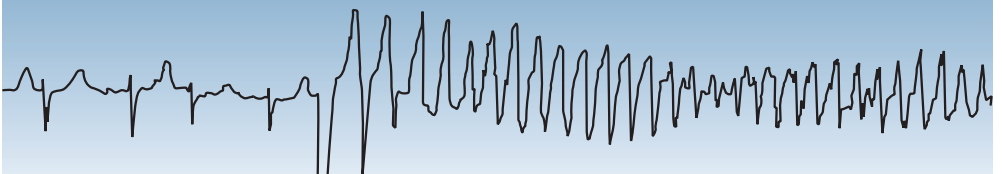
When the QT / QTc interval is prolonged¹⁶

- Clinically noteworthy changes in QT / QTc interval can be defined in terms of absolute QT / QTc intervals or changes from baseline
- Prolongation of QTc >500 msec is a threshold of particular concern
- Multiple analyses using different limits are useful to address this uncertainty:
Examples of different QTc prolongation thresholds are:
 - QTc interval >450 msec
 - QTc interval >480 msec
 - QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec

Figure 3. ECG trace showing TdP



What causes a prolonged QT interval?

- A prolonged QT interval occurs in both primary and secondary forms. The primary form is congenital,^{22,23} whereas the secondary form is acquired¹³
- Congenital long-QT syndrome is a rare disorder that is usually inherited and primarily affects children or young adults.²³ Individuals with this syndrome do not generally exhibit signs or symptoms, but fainting, arrhythmia and deafness may be seen^{24,25}
- Acquired forms of QT interval prolongation are generally due to underlying cardiovascular diseases, metabolic, endocrine, or electrolyte disorders
- A drug challenge to subjects with either congenital or acquired forms of QT prolongation may result in clinical symptoms. The first drug to be identified that affects the QT interval was quinidine, which was recognized as being associated with syncope in the 1920s.¹³ Since that time, a number of other drugs have been identified that may cause TdP; the most common of these are described in Table 3¹³

Table 3. Drugs associated with QT prolongation that may cause TdP ^{13,26}

Drug class	Examples
Antianginal	bepidil, perhexiline, ranolazine
Antiarrhythmic	amiodarone, dofetilide, sotalol, quinidine
Antibiotic / anti-infective	amphotericin, ciprofloxacin, clarithromycin, erythromycin,
Anticancer	arsenic trioxide, doxorubicin, tamoxifen, zorubicin
Antidepressant	citalopram, fluoxetine, paroxetine, trazodone, venlafaxine
Antihistamine	astemizole, fexofenadine, loratidine, terfenadine
Antimalarial	chloroquine, halofantine, quinine
Antimitotic	clotrimazole, luconazole, ketoconazole, myconazole
Antipsychotic	chlorpromazine, clozapine, haloperidol, quetiapine, risperidone, sertindole, thioridazine, ziprasidone
Others	atropine, cocaine, cisapride, fosphenytoin, lithium, methadone, sildenafil, spironolactone, tacrolimus, valproic acid,

Note: This table provides examples of drugs associated with QT prolongation but is in no way exhaustive. When considering prescribing an additional drug, please refer to its Summary of Product Characteristics to determine if it may place your patient at an elevated risk of QT prolongation.

- A number of additional clinical risk factors have been associated with an increased risk of drug-induced TdP and these are illustrated in Table 4. However, it is generally recognized that the list of risk factors associated with drug-induced TdP is incomplete and is not yet fully understood

Table 4. Risk factors for drug-induced TdP ^{1,3,13}

Female sex
Bradycardia
Recent conversion from atrial fibrillation, especially with a QT-prolonging drug
Congestive heart failure
Digitalis therapy
High drug concentrations (with the exception of quinidine)
Rapid rate of intravenous infusion with a QT-prolonging drug
Hypokalaemia
Severe hypomagnesaemia
Diabetes
Thyroid disorder
Baseline QT prolongation
Subclinical long-QT syndrome
Ion-channel polymorphisms

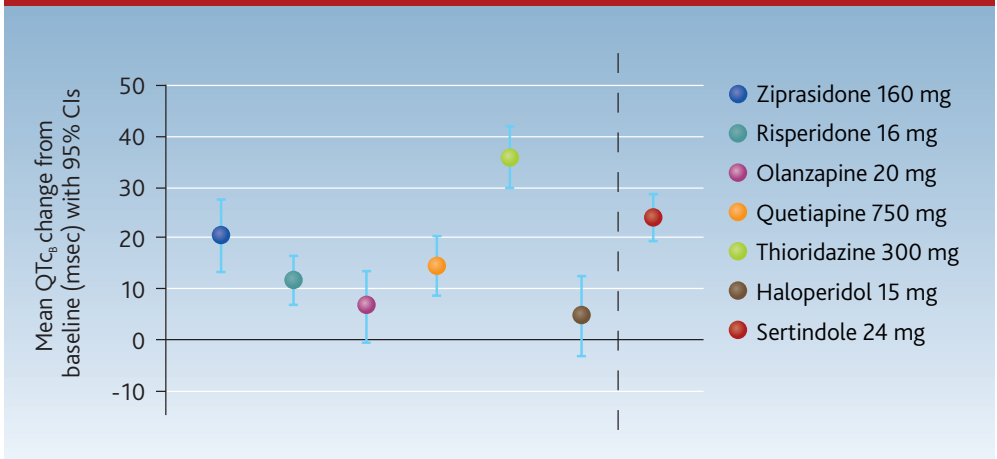
Mechanisms of QT prolongation

- The mechanisms of QT prolongation are complex. Genetic studies have identified at least six separate mutations in genes encoding potassium or sodium channels that can cause congenital long-QT syndrome. One of these in particular – the human ether-a-go-go-related gene (hERG) – is thought to be involved in many cases of drug-associated TdP ^{1,3,13,27}
- HERG encodes a potassium-channel protein that regulates a major repolarizing potassium current termed the delayed rectifier potassium current or I_{Kr}. ^{13,28,29} Most drugs that are associated with QT prolongation block I_{Kr}, although not all drugs with this property have been associated with TdP, suggesting that other factors may also be involved ¹³
- Importantly, the plasma concentration of drugs that block I_{Kr} can have a major impact on clinical consequences. For example, drugs like terfenadine have only a small effect on the QT interval in normal subjects, but a much greater effect when drug metabolism is reduced or blocked by drug interactions or hepatic disease ^{1,13}

QT prolongation during the treatment of schizophrenia

- For many years, there have been reports of increased risks of arrhythmias and SCD in association with antipsychotic use.^{30–33} Many antipsychotic medications have since been associated with a prolonged QT interval, which provides a possible explanation for these events^{3,34–36}
- The precise risks for cardiovascular adverse events and SCD with antipsychotics have yet to be determined, although QT prolongation has been observed with both old and newer agents (Figure 4)^{1,3,6,17,37}

Figure 4. Comparison of mean QTc change from baseline to steady state with high-dose treatment with different atypical antipsychotics.¹



Note, data for sertindole are from separate short-term studies using the maximum recommended dose (24 mg).

- There is no clear relationship between drug-induced QT prolongation and risks of arrhythmias / SCD. ^{1,3,13,38} For instance, the antiarrhythmic drug amiodarone induces a profound increase in the QT interval but the risk of TdP is recognized to be extremely low. ³⁹ Conversely, acute administration of haloperidol, a drug recognized not to increase the QT interval to a great extent, is widely reported to induce TdP under these conditions ^{40,41}
- Concerns about the risks of TdP and subsequent SCD have led to the withdrawal of some antipsychotic drugs from the market (e.g. droperidol). ¹ For other antipsychotic drugs, restricted prescribing guidelines have been introduced to address concerns regarding QT prolongation (e.g. thioridazine, ziprasidone, pimozide, sertindole), and in some cases, reductions in maximum recommended daily dosages have been introduced (e.g. haloperidol in the UK) ^{1,17}
- Regular ECG monitoring is mandatory in patients receiving sertindole. ⁷ In general, regular ECG monitoring may be considered good clinical practice when prescribing antipsychotics

Practical measures to minimize the antipsychotic medication

In order to minimize the risks of QT prolongation and arrhythmias with antipsychotic medications, the following measures should be undertaken:

- All patients under consideration for antipsychotic therapy should be questioned about family history of heart disease (particularly SCD) and should be asked if they have a known heart condition, have ever been prescribed medication for the heart / hypertension or have ever fainted. A pre-treatment ECG should be undertaken in patients answering yes^{1,3}
- Routine ECG monitoring is advised in patients with underlying metabolic and endocrine disorders (including thyroid disorders)
- Plasma electrolyte estimations should be undertaken in all patients to exclude abnormalities that might predispose to cardiac arrhythmias³
- In the following high-risk cases, routine ECG should be considered throughout treatment and access to expert cardiovascular opinion should be secured:^{3,13}
 - Patients with a family history of QT prolongation or SCD
 - Patients with pre-existing heart disease / cardiac symptoms
 - Elderly patients (particularly women)
 - Patients in whom polypharmacy is unavoidable or who are receiving drugs that prolong the QT interval
 - Patients predicted to require high doses of treatments over time
 - Patients with unreliable treatment adherence
 - Patients thought to be abusing other drugs
- Patients already receiving antipsychotics should be warned to report any symptoms such as palpitations, syncope or conditions that can cause hypokalaemia (e.g. gastroenteritis, diarrhoea and dehydration)¹³
- The following should be avoided:³
 - Combinations of antipsychotic treatments
 - Polypharmacy with drugs known to prolong the QT interval
 - Use of drugs known to inhibit relevant cytochrome isoenzymes

risk of QT prolongation with

- The use of depot antipsychotics should be considered carefully in view of their prolonged duration of action and potential for prolonged toxicity if poorly tolerated ³
- If a QTc interval of more than 500 msec is observed, treatment should be discontinued ^{3,7}
- Clinical symptoms such as heart pounding, palpitations, syncope or vasovagal symptoms during treatment should lead to a cardiovascular examination, including an ECG

Risk of QT prolongation and arrhythmias with sertindole

Sertindole should not be administered to patients: ⁷

- With uncorrected hypokalaemia / hypomagnesaemia
- With a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmias or bradycardia (<50 beats / min)
- With congenital long-QT syndrome, or a history of this disease, or with acquired QT prolongation:
 - QTc >450 msec in men
 - QTc >470 msec in women
- Receiving drugs known to significantly prolong the QT interval:
 - Class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
 - Some antipsychotics (eg. thioridazine)
 - Some macrolides (e.g. erythromycin)
 - Some antihistamines (e.g. terfenadine, astemizole)
 - Some quinolone antibiotics (e.g. gatifloxacin moxifloxacin)
- With severe hepatic disease
- Elderly patients (>65 years) without a thoroughly conducted cardiovascular examination

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