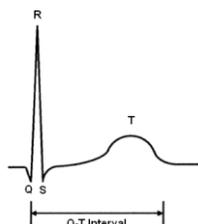


## Drug-Induced QT Interval Prolongation

In the past few years, much attention has been focused on drugs that prolong the QT interval and may trigger potentially fatal cardiac arrhythmias such as Torsade de Pointes ("twisting of the points"). Several drugs (e.g. cisapride and terfenadine) have been withdrawn from the world market because of their association with this rare form of cardiotoxicity. The US Food and Drug Administration and Australian Therapeutic Goods Administration recently advised patients and health professionals that high dose citalopram is associated with QT prolongation. In September 2011 the New Zealand datasheet for the funded brand of citalopram was modified. The maximum recommended dose of citalopram is now 40mg/day (20mg/day in the elderly and other risk groups).

### Understanding QT interval Prolongation



The QT interval represents the duration of the ventricular action potential and is measured from the beginning of depolarisation (Q wave) until the end of repolarisation (T wave).

QT prolongation is a sign of prolonged repolarisation of the ventricular myocardium, which is largely controlled by potassium channels.

With repeated prolonged repolarisation of sufficient extent, ventricular arrhythmias may develop.

QT prolongation is generally considered present when the QTc interval (i.e. the QT interval corrected for heart rate) is greater than 450 msec in men or 470 msec in women. Arrhythmias occur most often at intervals of 500 msec or more, usually in association with concomitant risk factors.

Torsade de pointes (TdP) is an uncommon variant of ventricular tachycardia and refers to a form of polymorphic ventricular tachycardia (VT) in the presence of a prolonged QT interval. It is usually self-limiting, but can degenerate into ventricular fibrillation, or rarely, sustained ventricular tachycardia. It may result in dizziness, syncope, cardiac arrest and occasionally death. There is no straightforward relationship between QT prolongation and TdP and/or ventricular fibrillation. If VT occurs with a normal QT interval, the term "polymorphic VT" is used.

### Congenital versus Acquired QT Prolongation

QT prolongation may be congenital or acquired. Congenital QT prolongation includes underlying gene mutations that result in ion channel malfunction and "congenital long QT syndrome". The acquired form of QT prolongation can be attributed to metabolic abnormalities (e.g., acute hypokalaemia), medical conditions (e.g. myocarditis, heart failure) and drugs.

### Drug-Induced QT Prolongation

Drug-induced QT prolongation is thought to relate to blockade of cardiac potassium channels. A lengthened QT is often seen with Class III antiarrhythmic agents (eg. sotalol, amiodarone) but may also be caused by other drugs. Drug-induced QT prolongation usually occurs within several days of starting the offending agent. Below are some drugs with reasonable evidence associating them with TdP (list not exhaustive). Several drugs prolong QT but at this time, lack substantial evidence for causing TdP. It is important to be aware of the strength of evidence associating the drug with TdP when assessing patient risk.

Table 1: Drugs generally accepted to have a risk of TdP\*

amiodarone	clarithromycin	flecainide	pimozide
chloroquine	domperidone	haloperidol	quinidine
chlorpromazine	erythromycin	methadone	sotalol

\* reference: [www.qtdrugs.org](http://www.qtdrugs.org)

### Predisposing Factors

The risk of developing arrhythmias at any given QT interval varies widely between patients. The risk for developing TdP when starting a QT prolonging agent is influenced by the specific drug and by the following predisposing factors:

- Bradycardia (<50 beats/min)
- Electrolyte disturbances (esp. hypokalaemia, hypomagnesaemia)
- Female gender
- Heart failure
- Hypoglycaemia
- Hypothyroidism
- Myocardial ischemia / infarction
- Renal or hepatic disease (ie. affecting drug clearance)
- Recent cardioversion
- Congenital long QT syndrome
- High drug concentrations

### Drug Interactions

Drug interactions play a major role in QT prolongation and may also increase the risk of TdP by the following mechanisms:

- 1) Two drugs may cause QT prolongation independently with an additive effect
- 2) One drug may decrease the clearance (and therefore increase the plasma concentrations) of another drug that prolongs the QT interval
- 3) One or more drugs may cause electrolyte disturbance, bradycardia or other effects that predispose the individual to the QT prolonging effects of another drug

### Prevention of Drug-Induced QT Prolongation

The QT prolonging effect of drugs can be minimised:

- by avoiding their use in patients with known risk factors
- addressing modifiable risk factors (electrolyte disturbances, glycaemic control, thyroid function, etc)
- close attention to appropriate dosing (dose-dependent)
- avoiding relevant drug interactions, particularly multiple drugs associated with QT prolongation
- ECG monitoring (baseline ECG should be considered and routinely monitored after initiation or dose increase of drugs that may prolong the QT interval. Dose reduction or discontinuation should be considered when the QTc is > 500 msec or if it increases > 60msec compared with baseline)

Patients should be counselled about the risk of QT prolongation and should be advised to seek medical attention if symptoms such as light-headedness, dizziness, palpitations, shortness of breath, or fainting occur.

### Citalopram

Health professionals should assess the risk of QT prolongation in patients taking citalopram and other selective serotonin reuptake inhibitors (SSRIs), as there may be a class effect. The evidence associating citalopram with TdP is similar to that for drugs listed in Table 1. However, abrupt cessation of SSRIs is associated with withdrawal symptoms and untreated depression/anxiety may also lead to poor health outcomes. The risk versus benefit must be weighed in each case. Where the risk of QT prolongation in an individual is small and other options have failed, higher doses of may be reasonable with appropriate monitoring.