Baxter K, editor. Stockley's Drug Interactions: Electronic edition. London: Pharmaceutical Press. Accessed via http://www.medicinescomplete.com/ 29/5/14

## Drugs that prolong the QT interval + Other drugs that prolong the QT interval

The concurrent use of more than one drug that prolongs the QT interval increases the risk of torsade de pointes, which may lead to life-threatening ventricular arrhythmias. The risk varies with different combinations of drugs that prolong the QT interval, and with the presence of other risk factors for this effect.

## Clinical evidence, mechanism, importance and management

If the QT interval on the ECG becomes excessively prolonged, ventricular arrhythmias can develop, in particular a type of polymorphic tachycardia known as torsade de pointes. On the ECG this arrhythmia can appear as an intermittent series of rapid spikes during which the heart fails to pump effectively, the blood pressure falls and the patient will feel dizzy and may possibly lose consciousness. Usually the condition is self-limiting but it may progress and degenerate into ventricular fibrillation, which can cause sudden death.

There are a number of reasons why QT interval prolongation can occur. These include:

- increasing age
- female sex
- congenital long QT syndrome
- cardiac disease
- thyroid disease
- some metabolic disturbances (hypocalcaemia, hypokalaemia, hypomagnesaemia)

Another important cause is the use of various QT-prolonging drugs including some antiarrhythmics, antipsychotics, antihistamines, antimalarials and others. [1,2] These drugs all appear to cause this effect by blocking the rapid component of the delayed rectifier (repolarisation) potassium channel.

At what degree of prolongation of corrected QT (QTc) interval torsade de pointes is likely to develop is uncertain. However a QTc interval exceeding

500 milliseconds is generally considered of particular concern, but this is not an exact figure. In addition, there is uncertainty about what constitutes an important change in QTc interval from baseline, although, in general, increases of 30 to 60 milliseconds should raise concern, and increases of over 60 milliseconds raise clear concerns about the potential for arrhythmias. Because of these uncertainties, many drug manufacturers and regulatory agencies contraindicated the concurrent use of drugs known to prolong the QT interval, and a 'blanket' warning was often issued because the QT prolonging effects of the drugs are expected to be additive. Regulatory guidance for the assessment of risk of a non-antiarrhythmic drug states that drugs causing an increase in mean QT/QTc interval of around 5 milliseconds or less do not appear to cause torsade de pointes. Data on drugs causing mean increases of around 5 milliseconds and less than 20 milliseconds are inconclusive, and some drugs causing this have been associated with proarrhythmic risk. Drugs with an increase of more than 20 milliseconds have a substantially increased likelihood of being proarrhythmic. [3,4] The extent of the drug-induced prolongation usually depends on the dose of the drug and the particular drugs in question.

**'Table 1'** below is a list of drugs that are known to prolong the QT interval and cause torsade de pointes. Note that this list is not exhaustive of all the drugs that have ever been reported to be associated with QT interval prolongation and torsade de pointes. For some of the drugs listed, QT prolongation is a fairly frequent effect when the drug is used alone, and it is well accepted that use of these drugs requires careful monitoring (e.g. a number of the antiarrhythmics). For other drugs, QT prolongation is rare, but because of the relatively benign indications for these drugs, the risk-benefit ratio is considered poor, and use of these drugs has been severely restricted or discontinued (e.g. astemizole, terfenadine, cisapride). For others there is less clear evidence of the risk of QT prolongation (e.g. clarithromycin, chlorpromazine). Drugs that have only been associated with isolated cases of torsade de pointes, and drugs that are commonly considered to cause QT prolongation, but for which there does not appear to be any published evidence to support this effect (e.g. **chloroquine**), are not usually included in this table. Specific reports of additive QT-prolonging effects with or without torsade de pointes are covered in individual monographs.

Drugs that do not themselves prolong the QT interval, but potentiate the effect of drugs that do (e.g. by pharmacokinetic mechanisms, lowering serum potassium, or by causing bradycardia) are not included in **'Table 1'**. The interactions of these drugs (e.g. azole antifungals with cisapride, astemizole, or terfenadine, and potassium-depleting diuretics with sotalol) are dealt with in individual monographs. However, note that some drugs, for example the macrolide

antibacterials, may cause QT prolongation by dual mechanisms: they appear to have both the intrinsic ability to prolong the QT interval, and they may inhibit the metabolism of drugs that prolong the QT interval. [5]

General references discussing the problems of QT-prolongation are given below. [6-15]

The consensus of opinion is that the concurrent use of drugs that have a high risk of prolonging the QTc interval should be avoided because of the risk of additive effects, leading to the possible development of serious and potentially life-threatening torsade de pointes. However, under certain circumstances (e.g. in the treatment of life-threatening arrhythmias) concurrent use may be unavoidable. In this situation close ECG monitoring, and a careful consideration of other risk factors present is essential. With drugs that have some risk of prolonging the QTc interval, some caution is appropriate, particularly in patients with other risk factors for QTc prolongation.

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**Table 1 Drugs causing QT prolongation and torsade de pointes**

| High risk | Some risk | Risk not categorised |
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| Antiarrhythmics, class Ia (ajmaline, cibenzoline, disopyramide, hydroquinidine, procainamide, quinidine) | Amisulpride | Amifampridine (no data but because of the arrhythmogenic potential of amifampridine other drugs that prolong the QT interval are contraindicated) |
| Antiarrhythmics, class III (amiodarone, azimilide, cibenzoline, dofetilide,† dronedarone, ibutilide,† sotalol†) | Bedaquiline (QTcF interval prolonged by 15.7 to 23.7 milliseconds) | Asenapine (QTc interval increased by 2 to 5 milliseconds with 5 to 20 mg daily; nevertheless some advise caution or avoiding other QT prolonging drugs) |
| Arsenic trioxide (40% of patients had a QTc interval greater than 500 milliseconds) | Chlorpromazine | Atomoxetine (No significant change in QTc interval from baseline in a study; however because of post-marketing reports of QT interval prolongation, some advise caution with other QT prolonging drugs) |
| Artemisinin derivatives (artemisinin, artemether/lumefantrine - 5% of patients had an asymptomatic prolongation of QTc intervals by greater than 30 milliseconds, with an actual QTc of greater than 450 milliseconds in males and greater than 470 milliseconds in females) | Citalopram (dose-dependent increase in QTcF interval of 7.5 to 18.5 milliseconds). | Boceprevir (no effect seen in studies; nevertheless UK manufacturer advises caution with other drugs that prolong the QT interval) |
| Halofantrine† | Dasatinib (increase in QTcF interval of 7 to 13.4 milliseconds) | Clarithromycin (increase in QTc interval of less than 5 milliseconds but because of rare case reports of torsade de pointes some advise caution with other QT prolonging drugs) |
| Haloperidol (risk increased in high doses and with intravenous use) | Droperidol† | |
| Ketanserin (30% of patients had an increase of greater than 30 milliseconds in a clinical trial) | Eribulin (QTcF interval prolonged by 11.4 milliseconds on day 8 of use) | |
| Mesoridazine† | Escitalopram (QTcF interval prolonged by 10.7 milliseconds with 30 mg daily) | |
| Pimozide† | Gatifloxacin (increase in QTc interval less than 10 milliseconds) | |
| | Iloperidone (12 mg twice daily increased QTc interval by 9 | |

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| Sertindole[†]<br><br>Thioridazine[†]<br><br>Vandetanib (QTcF prolonged by 35 milliseconds, with greater than 60 millisecond increase in QTcF interval in 36% of patients) | milliseconds; greater increases if metabolism inhibited)<br><br>Levomepromazine<br><br>Methadone (in doses greater than 100 mg)<br><br>Moxifloxacin (increase in QTc interval less than 10 milliseconds)<br><br>Nilotinib (QTc interval prolonged by 5 to 15 milliseconds)<br><br>Paliperidone (dose-dependent prolongation of 6.8 to 12.3 milliseconds)<br><br>Pasireotide (QTcF interval prolongation that equates to a 17.5 millisecond increase over placebo)<br><br>Pazopanib (QT interval of greater than 500 milliseconds in some patients)<br><br>Quinine (greater risk with higher doses and intravenous use)<br><br>Ranolazine (dose-related QTc interval prolonged by up to 15 milliseconds, or more if metabolism inhibited) | Clozapine (because of post-marketing reports of QT interval prolongation, some advise caution with other drugs that prolong the QT interval)<br><br>Erythromycin (greater risk with intravenous use)<br><br>Lapatinib (small, dose-dependent prolongation of the QTc interval; magnitude not stated)<br><br>Lithium (can increase the QT interval particularly if concentrations increased therefore some advise caution with other QT prolonging drugs)<br><br>Lofexidine (because of post-marketing reports of QT interval prolongation, some advise caution with other QT prolonging drugs)<br><br>Olanzapine (studies suggest no effect but UK manufacturer advises caution on the basis that other antipsychotics have QT prolonging effects)<br><br>Pentamidine (intravenous)<br><br>Prucalopride (no effect seen in studies; nevertheless UK manufacturer advises caution with other drugs that prolong the QT interval) |

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| | Romidepsin (QTc interval prolongation of 14.4 milliseconds in lymphoma patients)<br><br>Saquinavir boosted with ritonavir (QTcS interval increased by 18.9 milliseconds with 1 g/100 mg twice daily)<br><br>Sildenafil (QT interval prolonged by 6 milliseconds with 50 mg dose; not all studies have found an increase)<br><br>Sorafenib (QTcF interval prolonged by 9 milliseconds)<br><br>Sparfloxacin (QTcF interval prolonged by 10 milliseconds in clinical studies)<br><br>Sultopride[†]<br><br>Sunitinib (QTcF interval prolonged by 9.6 milliseconds)<br><br>Telaprevir (QT interval prolonged by 8 milliseconds)<br><br>Tolterodine (QTcF interval prolonged by up to 11.8 milliseconds)<br><br>Toremifene (Dose-related effect; QT interval prolonged by 21 to 26 | Quetiapine (the available data neither proves nor disproves an effect, therefore some advise caution with other QT prolonging drugs)<br><br>Rilpivirine (dose-related QT-prolongation occurs, which is considered unlikely to be clinically relevant at the recommended dose; however, because of the limited information manufacturers advise caution)<br><br>Risperidone (lack of direct evidence but note, paliperidone is a metabolite of risperidone and so some advise caution with other QT prolonging drugs)<br><br>Sodium stibogluconate (dose-related QT interval prolongation occurs; magnitude not stated, therefore some advise caution with other QT prolonging drugs)<br><br>Solifenacin (QTcF interval prolonged by 2 milliseconds with a 10 mg dose; however, because of post-marketing reports of QT interval prolongation, some advise caution with other QT prolonging drugs)<br><br>Spiramycin<br><br>Telithromycin (minimal effects seen in |

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| | milliseconds with 80 mg dose)<br><br>Tricyclics (prolongation of QTc interval greater than 10 milliseconds, most notable risk occurs with clomipramine, risk with other tricyclics largely seems to be in overdose)<br><br>Vardenafil (QTcF interval prolonged by 8 milliseconds with 10 mg dose)<br><br>Ziprasidone (QTc interval prolonged by about 10 milliseconds with 160 mg dose) | some studies, but others suggest an effect similar to clarithromycin in small proportion of patients)<br><br>Tizanidine (small *in vivo* studies suggest no increase in QT or QTc intervals; however, chronic toxicity studies in *dogs* have resulted in QT prolongation and therefore some advise caution with other QT prolonging drugs)<br><br>Trazodone (because of post-marketing reports of QT interval prolongation, some advise caution with other QT prolonging drugs)<br><br>Vinflunine (because of a few reports of QT interval prolongation, some do not recommend the use of other QT prolonging drugs)<br><br>Zotepine (dose-related QT prolongation said to occur, magnitude not stated)<br><br>Zuclopentixol (appears to cause QT prolongation in overdose; because of the known effects of other antipsychotics, some advise caution with other QT prolonging drugs) |
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[†]indicates drug suspended/restricted in some countries because of this effect
This list is not exhaustive