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162 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 ■ ■There is some controversy over the exact association between QTc and risk of arrhythmia. Very limited evidence suggests that risk is exponentially related to the extent of prolongation beyond normal limits (440ms for men; 470ms for women), although there are well-known exceptions which appear to disprove this theory24 (some drugs prolong QT without increasing dispersion). Rather stronger evidence links QTc values over 500ms to a clearly increased risk of arrhythmia.25 QT intervals of >650ms may be more likely than not to induce torsades.26 Overall, despite some uncertainties, QTc determination remains an important measure in estimating risk of arrhythmia and sudden death. ■ ■Individual components of the QT interval may have particular importance. The time from the start of the T wave to T-wave peak has been shown to be an important aspect of QT prolongation associated with sudden cardiac deaths;27 T-wave peak to end interval may also be predictive of arrhythmia.12 ■ ■QTc measurements and evaluation are complicated by: ■ ■difficulty in determining the end of the T wave, particularly where U waves are present (this applies to both manual and self-reading ECG machines)25 ■ ■normal physiological variation in QTc interval: QT varies with gender, time of day, food intake, alcohol intake, menstrual cycle, ECG lead, etc.22,24 ■ ■variation in the extent of drug-induced prolongation of QTc because of changes in plasma levels. QTc prolongation is most prominent at peak drug plasma levels and least obvious at trough levels.22,24 Other ECG changes Other reported antipsychotic-induced changes include atrial fibrillation, giant P waves, T-wave changes and heart block.24 Quantifying risk Drugs are categorised here according to data available on their effects on the cardiac QTc interval as reported, mostly using Bazett’s correction formula (Table 1.35). ‘No- effect’ drugs are those with which QTc prolongation has not been reported either at therapeutic doses or in overdose. ‘Low--effect’ drugs are those for which severe QTc prolongation has been reported only following overdose or where only small average increases (<10ms) have been observed at clinical doses. ‘Moderate-effect’ drugs are those which have been observed to prolong QTc by >10ms on average when given at normal clinical doses or where ECG monitoring is officially recommended in some circumstances. ‘High-effect’ drugs are those for which there is extensive average QTc prolongation (usually >20ms at normal clinical doses). As outlined above, effect on QTc may not necessarily equate directly to risk of TdP or sudden death,28 although this is often assumed.29 (A good example here is ziprasidone – a drug with a moderate effect on QTc but with minimal evidence of cardiac toxicity.30) Also, categorisation is inevitably approximate given the problems associated with QTc measurements. Lastly, keep in mind that differences in the effects of different antipsychotics on the QT interval rarely reach statistical significance even in meta-analyses.31

Schizophrenia and related psychoses CHAPTER 1 Outside these guidelines, readers are directed to the RISQ-PATH study,32 which provides a scoring system for the prediction of QT prolongation (to above normal ranges) in any patient. RISQ-PATH has a 98% negative predictive value, so allowing a reduction in monitoring in low-risk patients. The RISQ-PATH method uses CredibleMeds categorisation for drug effects on QT – this, too, is recommended.33 Table 1.35 Antipsychotics – effect on QTc.12,22,24,34–59 Effect on QTc Drug No effect Brexpiprazole Cariprazine Lurasidone Lumateperone* Low effect Aripiprazole** Asenapine Clozapine Flupentixol Fluphenazine Perphenazine Prochlorperazine Olanzapine† Paliperidone Risperidone Sulpiride Zuclopenthixol Moderate effect Amisulpride‡ Chlorpromazine Haloperidol Iloperidone Levomepromazine Melperone Pimavanserin Quetiapine Ziprasidone High effect Pimozide Sertindole Unknown effect Loxapine Pipotiazine Trifluoperazine * Limited clinical experience (association with QT prolongation may emerge). ** One case of TdP reported,60 two cases of QT prolongation61,62 and an association with TdP found in database studies.63,64 Healthy volunteer data suggest aripiprazole causes QTc prolongation of around 8ms.65 Aripiprazole may increase QT dispersion.66 Low-dose aripiprazole has no effect on QT when added to another antipsychotic.67 † Isolated cases of QTc prolongation38,68 and has effects on cardiac ion channel, IKr.69 Other data suggest no effect on QTC.24,36,37,70 ‡ TdP common in overdose,26,71 strong association with TdP in clinical doses.63

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