Eur Child Adolesc Psychiatry (2007)
16:33–47 DOI 10.1007/s00787-006-0573-0

ORIGINAL CONTRIBUTION

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The QT interval and psychotropic medications in children

Recommendations for clinicians

Accepted: 26 June 2006
Published online: 29 August 2006

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Abstract The use of psychotropic medications in children has increased significantly in the last few years. There have been several case reports of sudden death in children taking specific psychotropic medications. Fears that these deaths might have been caused by ventricular arrhythmias have been enhanced by reports of electrocardiographic abnormalities, including prolongation of the QTc interval, in patients taking these medications. Several factors including genetic susceptibility, pre-existing cardiac disease, abnormalities of drug clearance and concomitant use of other medications known to affect the QTc interval can increase the susceptibility of the heart to conduction abnormalities. This article discusses the potential of particular psychotropic drugs to prolong the QTc interval in children, and examines other factors that may contribute to conduction abnormalities. We aim to provide clear clinical recommendations for the prescription of these drugs and the monitoring of children taking them.

Key words psychotropic medications – QTc prolongation – arrhythmia – prescribing – children

Introduction

The use of psychotropic medications in children has increased significantly in the last few years [9, 14, 26, 37, 110, 142]. In addition to their use for the treatment of psychoses in children, antipsychotic drugs are increasingly being used for nonpsychotic disorders such as autism, ADHD, mood disorders, aggressive behaviour, acute behavioural dyscontrol and disruptive behaviours [4, 26, 53, 65, 82, 109, 111, 118, 134]. Zito et al. and Rappley et al. also report an increase in the rate of prescription of psychotropic medications to pre-school children [98, 142]. In addition, both in the US and Europe, psychotropic medications are increasingly being prescribed by both paediatricians and general practitioners in addition to child psychiatrists [84]. Despite this increase in the rate of prescription, studies have shown that self-assessed levels of competence in prescription practice among prescribers of psychotropic medications is low, with many feeling they have inadequate information in relation to drug safety [16, 83, 84, 121]. Measures have been taken to reduce this in some areas, for example with the TRAAY guidelines (Treatment Recommendations for the use of Antipsychotics for Aggressive Youth) [92, 112], however a considerable shortfall still exists. Few psychotropic medications have been extensively studied in children, reflecting the fact that a large proportion of drugs used in paediatrics in general have undergone little clinical research in children [1, 13, 19].

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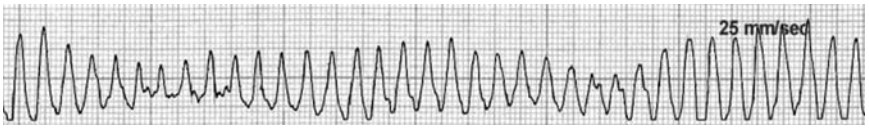
Fig. 1 Torsades de Pointes



In the last 20 years, there have been many deaths in children taking tricyclic antidepressants both at therapeutic doses and in overdose [5, 10, 96, 101, 126, 128, 129]. While no firm evidence links these deaths specifically to the effects of drugs on the QT interval, suspicion must remain high given the many reports of conduction abnormalities produced by these medications. In the last 10 years, the commonest reason for denial or withdrawal of a drug licence in the US is the propensity for the drug to prolong the QT interval [74]. Several psychotropic drugs have been implicated [100, 135].

In 1999, the American Heart Association published guidelines for the cardiovascular monitoring of children and adolescents receiving psychotropic drugs [45]. However, since then, and as the use of newer psychotropic medications increases, many more case reports of toxicities have appeared [11, 17, 22, 32, 35, 42, 57, 69, 128]. This article aims to provide clear up-to-date clinical guidelines on risk assessment and cardiovascular monitoring for those prescribing psychotropic medications for children.

Physiology

The cardiac action potential is produced by the flow of ions through channels in the cell membrane. The *inflow* of positively charged ions is responsible for cardiac depolarisation, and repolarisation is caused by the net *outflow* of positively charged ions from the cell. On a surface ECG, the QRS complex depicts cardiac depolarisation and the T wave reflects repolarisation. A delay in cardiac repolarisation will lead to prolongation of the QT interval on the ECG. Prolongation of the QT interval is a risk factor for the development of ventricular arrhythmias, and in particular an arrhythmia called "Torsades de Pointes" or twisting of the points, describing its appearance on the surface ECG (Fig. 1).

ECG measurements

The QT interval is measured from the start of the QRS complex to the end of the T-wave (see Fig. 2). Since children of different ages have different resting heart rates, the QT interval can vary. There is, however, a standardised way to correct for these variations in heart

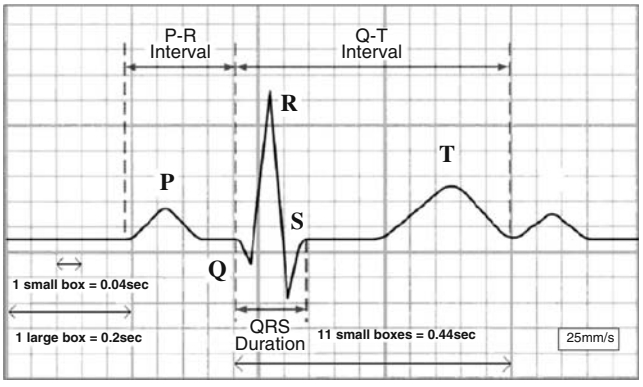


Fig. 2 Basic ECG measurements. Note standard paper speed of 25 mm/s

rate. The QT interval, when corrected for heart rate (QTc), is a more reliable indicator of abnormally prolonged repolarisation. QTc should always be measured in lead II to minimise error. Automated ECG machines will usually calculate the QT and QTc interval, and although most will do so accurately, given variations in T wave morphology, it is advisable for the clinician to measure the intervals manually. The QTc can be calculated manually using the formulae:

$$QTc = \frac{QT}{\sqrt{R\text{-}R}} \qquad QTc = \frac{QT}{\sqrt[3]{R\text{-}R}}$$

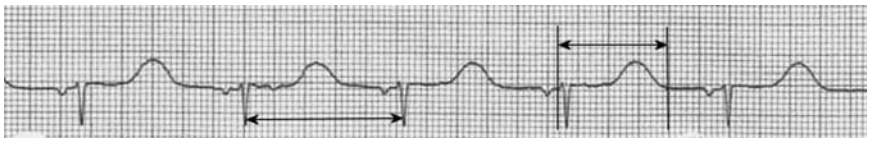
Bazzet Correction — Frederica Correction

where R–R is the distance between two R waves i.e. between the peaks of two QRS complexes (see Fig. 3). The QTc interval is measured in milliseconds, whereas the R–R interval is measured in seconds. The Bazett correction is the most commonly used and easy to apply but tends to slightly overestimate the QTc interval especially at extremes of heart rate. The Frederica correction uses a cubed root and thus has less error, and is preferred, but is used less because of the difficulty of the cubed root for many people. Several different methods of correction exist, none of which are consistently reliable at all heart rates. What is important is that a rate correction is used, and that the same one is used consistently.

Normal values

The upper limit of normal for the QTc interval is defined as 450 ms in males and 460 ms in females [113].

Fig. 3 Measuring RR and QT interval



However, the relationship between absolute QTc interval and the risk of Torsades de Pointes is not linear. Studies of the congenitally inherited version of long QT syndrome have shown a striking variation in QTc interval even between family members with the same mutation [107]. The QTc interval is also affected by age, sex (longer in females), time of the day and proximity to meals and exercise [60, 63, 70]. Prolongation of the QTc interval beyond 500 ms [113] and an increase in QTc of greater than 60 ms from baseline [47] have both been shown to predict Torsades de Pointes. The risk of developing ventricular arrhythmia secondary to prolongation of the QTc interval appears to be multifactorial. Hence, while an arbitrary upper limit is placed on the QTc interval, other factors, as mentioned above, need to be considered when assessing the risk of developing a ventricular arrhythmia in a patient taking a given medication.

Genes encoding for three main ion channels responsible for cardiac repolarisation have been found [25, 72]. Mutations in these genes are responsible for familial long QT syndrome. One of these genes, the Human *Ether-a-go-go* Related Gene (HERG) encodes the main conduit for the efflux of positive ions during repolarisation—the rapid component of the delayed rectifier potassium channel (IKr) [107]. Although IKr malfunction may also be caused by electrolyte imbalance and autonomic dysfunction, the commonest cause is the administration of medications [39]. A wide range of medications are known to prolong cardiac repolarisation and thus QT interval (Table 1).

Many factors, some poorly understood, can affect the physiologic mechanisms that maintain normal cardiac repolarisation [41, 119]. The concept of "reduced repolarisation reserve" [102] has been used as an umbrella term to encompass these factors, and suggests that the physiology of cardiac repolarisation varies between patients. Some apparently healthy subjects will be more susceptible to prolongation of the QT interval as a result of minor physiological or biochemical changes such as drug ingestion [103]. This enhanced susceptibility to QT prolongation may not be apparent on the ECG in the basal state.

With increases in clinical experience and with advances in molecular cardiology, it is evident that the QT interval on the surface ECG is a crude variable and occasionally a misleading measure of the "well-being" of cardiac repolarisation. It is undoubtedly true that, in general, (a) there is a relationship between prolongation of the QT interval on the ECG and susceptibility to malignant ventricular arrhythmias (Torsades de Pointes) and sudden death; and (b) the more abnormal the QT interval and the more bizarre looking the T-wave, the greater the risk of developing Torsadse de Pointes. However, occasionally a repolarisation abnormality (and hence susceptibility to Torsades de Pointes) will not produce a prolonged QT interval on the ECG, or QT prolongation may be intermittently present, depending on fluctuations in blood chemistry, neurohormonal and autonomic balance.

Table 1 Some commonly prescribed nonpsychiatric drugs that may (1) cause Torsades de Pointes and (2) interact significantly with other medications

Torsades de Pointes	Drug interactions
Amiodarone	Amiodarone
Chloral hydrate	Chlorpheniramine
Chloroquine	Cimetidine
Clarithromycin	Clarithromycin
Domperidone	Erythromycin
Erythromycin	Grapefruit juice
Fosphenytoin	Itraconazole
Methadone	Ketoconazole
Ondansetron	Ranitidine
Salmeterol	
Sotalol	
Tacrolimus	
Voriconazole	

Since QT interval prolongation is only a mediocre surrogate for risk of Torsades de Pointes, the phenomenon of QT dispersion and its risk for ventricular arrhythmia has been examined. QT dispersion is a measure of the variation in the QT interval (defined as the difference between maximum and minimum QT interval duration). Unfortunately, like QT interval prolongation it has proved to be in inexact predictor of Torsades de Pointes [115].

Although Torsades de Pointes is often a transient arrhythmia causing palpitations, equally it can be prolonged leading to syncope and/or seizures. Depending on the duration of Torsades de Pointes and one's genetic pre-disposition, it may progress to ventricular fibrillation and sudden death. The overall mortality from Torsades de Pointes is 10–17% in the adult population [115].

Additional background risk factors

Genetic pre-disposition

Two clinical phenotypes of the long QT syndrome (LQTS) have been recognised: Jervell and Lange-Nielsen syndrome [61] – a recessively inherited syndrome associated with sensorineural deafness, and Romano Ward Syndrome [104, 133]—a more common dominantly inherited form without deafness. To date, six genes have been implicated in the pathogenesis of LQTS. Three loci are responsible for the majority of cases; chromosome 11p15.5 (LQT1), chromosome 7q35-36 (LQT2), chromosome 3p21-24 (LQT3).

The classical symptoms of these conditions include syncope, unexplained seizures (e.g. atypical seizure history with normal EEG) and sudden death. Triggers are variable but include fright, loud noises, exercise, playing in water and bradycardia. The addition of a further risk factor for QT prolongation (such as drug ingestion) can be very dangerous in these children, so it is important to elicit a family history of unexplained seizures, syncope or sudden death, especially in the above settings.

Structural heart disease

Children with structural heart disease, whether corrected or not, have an increased prevalence of cardiac conduction abnormalities. Ventricular repolarisation abnormalities and ventricular dysrhythmias are particularly prominent in corrected tetralogy of fallot and children undergoing Fontan correction (univentricle physiology). Clinicians should be cautious when prescribing drugs that may prolong the QT interval in these children.

Electrolyte abnormalities

Normal cardiac repolarisation is dependant on a stable electrolyte environment. Alterations in this environment are well known to cause dysrhythmia. Common causes include intercurrent illness (diarrhoea and vomiting), pre-existing biochemical abnormalities (e.g. renal tubular acidosis) or the use of medication (e.g. diuretics). Electrolyte abnormalities can potentiate the adverse effects of QT prolonging drugs and lead to malignant arrhythmias.

Other medications

Psychotropic drugs that may have a mild effect on the ECG in therapeutic doses can cause clinically significant QT changes at high therapeutic doses and in both acute and chronic overdose. The administration of medications that may interact with or inhibit the clearance of QT prolonging drugs can cause excessive lengthening of the QT interval and a significantly increased risk of arrhythmia. There are many case reports of life-threatening arrhythmias in patients on psychotropic medications caused by the co-administration of drugs that interfere with their metabolism [117]. The combination of antipsychotic and antidepressant mediactions is a notable example [51, 85, 89, 106]. Recent US data indicates that the use of multiple psychotropic medications in children is increasing [33]. In their study, dosReis et al. [33] found that multiple psychotropic drug use occurred in nearly one third of patients being treated with any psychotropic medications. Given the fact that psychotropic drug combinations form the majority of cases of QTc prolongation occurring with multi-drug combinations, this is a worrying statistic.

The cytochrome P450 system

The cytochrome P450 (CYP450) system is responsible for the oxidation and metabolism of over 90% of drugs. Five isoenzymes of CYP450 account for most metabolising activity: 3A4, 2C19, 1A2, 2C9 and 2D6, the 3A4 isoenzyme being involved in the widest range of drug metabolism [114]. Many psychotropic drugs are metabolised by the 3A4 isoenzyme system. If another medication which is also metabolised by 3A4 is administered concomitantly, it may competitively inhibit the metabolism of the psychotropic medication causing inadvertent overdose and an increased risk of QT prolongation. This is the case for each of the isoenzymes of the CYP450 system, so dangerous interactions can often be avoided by checking which isoenzyme is responsible for metabolism of a particular medication (See Table 2 or visit www.drug-interactions.com). Common drugs inhibiting the 3A4 system include macrolide antibiotics (erythromycin and clarithromycin), azole antifungals (itraconazole and ketoconazole) and antiretrovirals. In one study, concurrent use of these inhibitors was reported in 37–56% of patients with Torsades de Pointes in association with terfenadine and cisapride [115]. The 2D6 isoenzyme system is also important for psychiatrists, as many psychiatric drugs including tricyclic antidepressants, haloperidol and risperidone are metabolised by the 2D6 system, of which fluoxetine is a potent inhibitor.

There is considerable variation among different individuals in expression of genes coding for CYP and other metabolic enzyme pathways, one of the reasons for varying levels of drug efficacy and side effects

Table 2 Common inhibitors, inducers and substrates for the cytochrome p450 system

Inhibitors		Inducers	Substrates		
1A2	**3A4,5,7**	**1A2**	**1A2**	**2C19**	**3A4,5,7**
Cimetidine	Delaviridine	Tobacco	Theophylline	Progesterone	Clarithromycin
Fluoroquinolones	Indinavir		Clozapine	Omeprazole	Erythromycin
Fluvoxamine	Nelfinavir	**2B6**	Imipramine	Lansoprazole	Quinidine
	Ritonavir	Phenobarbitone	Mexiletine	Pantoprazole	Alprazolam
2C9	Saquinavir	Rifampicin	Naproxen	Diazepam	Diazepam
Amiodarone	Amiodarone			Phenytoin	Midazolam
Fluconazole	Cimetidine		**2B6**	Phenobarbitone	Cyclosporine
Isoniazid	Clarithromycin	**2C9**	Methadone	Amitriptyline	Tacrolimus
	Diltiazem	Rifampicin	Bupropion	Clomipramine	Indinavir
2C19	Erythromycin	Ethanol	Cyclophosphamide	Cyclophosphamide	Ritonavir
Fluoxetine	Fluvoxamine	Isoniazid	Ifosfamide		Saquinavir
Fluvoxamine	Grapefruit juice			**2D6**	Cisapride
Ketoconazole	Itraconazole	**3A4,5,7**	**2C9**	Metoprolol	astemizole
Lansoprazole	Ketoconazole	Carbamazepine	Diclofenac	Propafenone	Chlorpheniramine
Omeprazole	Mibefradil	Phenobarbitone	Ibuprofen	Timolol	Amlodipine
	Nefazodone	Phenytoin	Piroxicam	Amitriptyline	Diltiazem
2D6	Verapamil	Rifabutin	Tolbutamide	Clomipramine	Felodipine
Amiodarone		Rifampicin	Glipizide	Desipramine	Nifedipine
Chlorpheniramine		St. John's wort	Irbesartan	Imipramine	Verapamil
Cimetidine			Celecoxib	Paroxetine	Atorvastatin
Clomipramine			Fluvastatin	Haloperidol	Cerivastatin
Fluoxetine			Naproxen	Risperidone	Lovastatin
Haloperidol			Phenytoin	Thioridazine	Simvastatin
Methadone			Sulfamethoxazole	Codeine	Buspirone
mibefradil			Tolbutamide	Dextromethorphan	Haloperidol
Paroxetine			Warfarin	Flecainide	Methadone
Quinidine				Mexiletine	Pimozide
Ranitidine				Ondansetron	Sildenafil
Ritonavir				Tramadol	Trazodone
Disulfiram				Venlafaxine	Vincristine
				Paracetamol	
				Ethanol	

A full list is available at www.drug-interactions.com

among seemingly homogenous patient groups. Analysis of this genetic basis of differential drug handling may enable us in the future to tailor medications for particular individuals. In a study on CYP2D6 genotypes among psychiatric patients taking risperidone, those with only one active gene were shown to have higher plasma drug levels and more QTc prolongation than those with two active genes [78].

Psychotropic medications that may prolong QT

Our primary safety concern when prescribing psychotropic medications to children must be the avoidance of malignant cardiac arrhythmia (Torsades de Pointes). With further clinical experience and prompt reporting of side-effects of psychotropic medications in children, a clearer picture as to the absolute risk these drugs pose will become available. A review of the literature currently available shows a paucity of studies dealing specifically with electrocardiographic safety of psychotropic medications in children. The University of Arizona Centre for Education and Research on Therapeutics (Arizona CERT) maintains a database of drugs that have been reported to cause Torsades de Pointes and/or QT prolongation. It relies on case reports from clinicians and is regularly updated (www.torsades.org). It should be noted that it is not specific for children.

Case reports of side-effects from particular medications must be interpreted in light of their frequency of use. A handful of case reports of toxicity involving a rarely used agent is of much greater concern, and indicates a higher risk, than the same number of case reports involving a widely prescribed agent. By the same token, assurance as to the clinical safety of newly released agents cannot be fully realised until considerable experience exists with their use, and thus until this is the case, prescribers of these medications need to be wary of unexpected toxicities.

Atypical antipsychotics

Risperidone has been shown in vitro to cause delayed ventricular repolarisation in human myocardial cells [43]. Some studies in adults have shown small

but significant degrees of QTc prolongation with **risperidone** at regular and high dose [48, 141], whereas others with a larger cohort showed no prolongation at regular doses [21]. There is no clear evidence linking **risperidone** with Torsades de Pointes. In overdose, there are some reports of QTc prolongation in children [42, 97], but also many reports of normal ECGs with significant overdose [18].

Olanzapine is a commonly used atypical antipsychotic. An early study involving olanzapine suggested significant QTc prolongation at therapeutic doses [23]; however, this has not been supported by subsequent reports. In a meta-analysis of four studies involving the use of olanzapine in 2,700 adult patients, Czekalla et al. showed that olanzapine does not contribute to QTc prolongation to a degree that resulted in potentially fatal ventricular arrhythmias [27]. QTc prolongation in a 28-year-old woman receiving higher doses of olanzapine [31] and a middle aged woman with Wolff–Parkinson–White syndrome have been reported [125]. Olanzapine seems to be safe from a cardiovascular point of view in overdose, with the vast majority of side-effects being CNS related.

Quetiapine, like clozapine, has a tendency to cause tachycardia in high therapeutic doses and overdose. There have been a number of case reports of QTc prolongation from overdose with quetiapine in adults and children [8, 97]. Harrigan et al. showed a mean increase in baseline QTc of only 6 ms in 27 patient receiving **quetiapine** [48]. One case report of Torsades de Pointes occurring in an adult with multiple medical and psychiatric problems on low dose **quetiapine** exists, however there was significant hypomagnesaemia and insufficient evidence to implicate **quetiapine** [132]. There is no evidence to suggest significant QTc prolongation in therapeutic doses in children.

Ziprasidone is another of the newer atypical antipsychotic agents. Pre-marketing studies by the manufacturer and a subsequent manufacturer sponsored trial [48] suggested a propensity towards modest QTc prolongation (mean increase over baseline of 17 ms in 35 patients). A recent study of 20 children on low dose ziprazidone (≤40 mg/day) found a mean increase in QTc of 28(±26) ms with no relationship to dose [12]. Post-marketing literature has revealed no cases of Torsades de Pointes or sudden death at therapeutic doses in either adults or children. Overdose with ziprasidone alone has been described in a 17 month old child who ingested 400 mg and developed a tachycardia of 240 beats per minute and minor QTc prolongation (480 ms) [17]. There are a handful of case reports in both adults and children of QTc prolongation in overdose with ziprasidone and other psychiatric medications in combination [11, 17].

Aripiprazole is a newer atypical antipsychotic that works as a partial agonist at the D2 receptor. Thus far, QTc prolongation has not been described in either animal models, adults or children. Overdose of aripiprazole has been described in children leading to significant CNS depression but no cardiovascular effects [79].

Clozapine was the first of the atypical antipsychotic medications to become available. Its major side effect is agranulocytosis, which has relegated its use to second line. Dose dependent QTc prolongation has been shown in both animals and adults [62, 77]. One case report of Torsades de Pointes could be found in the literature, however the presence of significant comorbidity makes it unlikely that clozapine induced the arrhythmia [130]. Tachycardia has been described in both therapeutic doses and overdose [123] as has pseudophaeochromacytoma syndrome [66]. An increased risk of sudden death with overdose has been shown [127].

Typical antipsychotics

The phenothiazines **chlorpromazine**, **thioridazine**, **mesoridazine**, **perphenazine**, **trifluoperazine** and **fluphenazine** may all cause tachycardia and hypotension from anticholinergic effects. QTc interval prolongation is well described with all of the phenothiazines [100, 124], and some have been reported to cause broad complex tachycardias including Torsades de Pointes [100].

In overdose, the phenothiazines can cause supraventricular, ventricular tachycardia and Torsades de Pointes [36, 52]. **Mesoridazine** and **thioridazine** have been shown to produce dose dependant QTc prolongation and are particularly cardiotoxic in overdose [28]. Melleril® (thioridazine) was discontinued worldwide in June 2005.

The butyrophenones **haloperidol** and **droperidol** have both been shown to cause QTc prolongation at therapeutic doses [44]. Numerous reports of Torsades de Pointes exist with both **haloperidol** [54, 59, 67, 90, 94] and **droperidol** [46, 86]. **Droperidol** has a US Federal Drug Administration (FDA) "black box" warning relating to its potential to prolong the QTc interval and was withdrawn from the UK market in 2001.

Pimozide has been shown to cause significant QTc prolongation in therapeutic use and overdose [40, 116]. It has been clearly implicated in causing Torsades de Pointes [40]. Recent in vitro work has documented its effects on the rapid component of the delayed rectifier potassium channel of the cardiac

myocyte producing prolongation of repolarisation [34, 62].

Pipamperone, used predominantly in central Europe has been associated with a case report of QTc prolongation in overdose in a child [15] but not at therapeutic doses. Introduced initially in the 1970s, little specific cardiac safety information exists for pipamperone.

Tricyclic antidepressants

Although largely replaced in the treatment of depression in children, tricyclic antidepressants are still used for this indication, as well as their use in cases of chronic pain and nocturnal enuresis. Sudden death has been reported in both adults and children taking tricyclic antidepressants [96]. Prolongation of the QTc interval by therapeutic doses of **desipramine**, **amitriptyline**, **nortriptyline** and **imipramine** in children is well established [45, 138]. Although no specific link between QTc prolongation and sudden death due to the arrhythmia in these children has been found, the index of suspicion must remain high.

Selective Seretonin Reuptake Inhibitors (SSRI)

The SSRI in general have a very low risk of causing Torsades de Pointes, but this risk may be increased when combined with the above mentioned risk factors (e.g. structural heart disease, electrolyte abnormalities, congenital long QT syndrome etc.). It should be noted in addition that SSRIs may inhibit one or more hepatic enzymes and therefore increase levels of co-administered medications. In a review of 469 SSRI overdoses, Isbister et al. found that citalopram was significantly more likely to prolong QTc than the other agents in this category, with sertraline carrying the lowest risk [56].

Fluoxetine has been reported to cause prolonged QTc, T wave changes and syncope in therapeutic doses in adults in a few case reports [99, 131, 140]. However, given the frequency of use of flouxetine and the lack of QTc prolongation in pre- and post-marketing efficacy studies, QTc prolongation should be seen as a very rare phenomenon. It should be noted that fluoxetine is a potent inhibitor of the CYP2D6 system and can cause significant toxicity from accumulation of other medications, especially imipramine [89].

Citalopram has shown no prolongation of the QTc at therapeutic doses in adults or children, but many reports describe it in overdose [56, 64]. Isbister et al. found that 68% of cases of citalopram overdose had a QTc >440 ms [56]. Citalopram may also cause bradycardia and hypotension in therapeutic doses and overdose [58, 105].

A recent review of electrocardiographic data from randomised trials of **paroxetine** produced by the manufacturer showed no QTc prolongation in 200 otherwise healthy children [68]. **Paroxetine** has been reported to prolong QTc in high risk adults [38]. There is no evidence that paroxetine causes Torsades de Pointes.

The cardiac safety of **sertraline** has been demonstrated in children and adolescents [139]. A combination of sertraline and pimozide was shown to have no effect on QTc interval in healthy adult volunteers [3]. There have been no reports of significant cardiac adverse events from several randomised trials of sertraline use in children. There is one case report of QTc prolongation with combined sertraline and benzodiazepine overdose in combination in an adult [29].

Fluvoxamine has been shown in a number of efficacy studies to have no significant effect on the QTc interval [49, 50, 71]. In a guinea pig model, fluvoxamine showed minimal QTc prolongation of <10 ms at high doses [91]. Overdose of fluvoxamine seems to be relatively safe, with rare case reports of bradycardia but not QTc prolongation [6, 73]. Fluvoxamine is a weak inhibitor of CYP2D6, a moderate inhibitor of CYP2C19 and CYP3A4 and a potent inhibitor of CYP1A2 so care must be taken with co-prescription.

New antidepressants

Bupropion has not been associated with prolongation of the QTc interval in therapeutic doses but may cause QT prolongation in overdose in adults [11]. Tachycardia may be associated with overdose and can make accurate calculation of QTc difficult [55].

Venlafaxine has been shown to produce widening of the QRS complex and ventricular tachycardia in overdose [24, 93]. There is one report of QTc prolongation in an elderly woman receiving therapeutic doses of **venlafaxine** [75].

Trazadone has been shown to prolong the QTc interval and cause arrhythmias including Torsades de Pointes in overdose [7, 30, 76]. At therapeutic doses, it has been shown to produce ventricular arrhythmias in adults in combination with both desipramine and amiodarone [81, 95]. Reports of QTc prolongation at therapeutic doses in adults or children could not be found.

Nefazodone has been reported to cause prolongation of the QTc and Torsades de Pointes in adults and adolescents as a result of drug–drug interactions [57, 120], but no reports exist in children. Of note,

nefazodone is an inhibitor of the cytochrome P450 (3A4) system and may restrict metabolism of concurrently administered drugs. **Nefazodone** has been withdrawn from the European market due to concerns over hepatic toxicity.

Mood stabilisers

Lithium is one of the most commonly used mood stabilisers. In adults, asymptomatic nonspecific T-wave changes, prolongation of the QTc interval, sinus node dysfunction, atrial flutter, atrioventricular block, ventricular tachycardia, ventricular fibrillation, and interstitial myocarditis have all been reported. Case reports of sinus node dysfunction, cardiomyopathy and ventricular arrhythmia have been described in overdose in children; however, no consistent prolongation of the QTc interval at standard doses has been reported [87]. Anticonvulsants medications such as **lamotrigine**, **topiramate**, **gabapentin**, **carbamazepine** and **valproic acid** are also used as mood stabilisers—none of these drugs is reported to cause prolonged QTc or Torsades de Pointes. No specific cardiovascular monitoring is indicated.

Drugs used for ADHD

Methylphenidate, **dextroamphetamine**, **amphetamine** and **pemoline** are stimulants used in the treatment of ADHD. None of these medications have been shown to prolong the QTc interval or induce Torsades de Pointes. **Clonidine**, an alpha agonist is often used in conjunction with methylphenidate in the treatment of ADHD. ECG abnormalities have been described in children taking **clonidine** [20]. **Clonidine** stimulates central α_2-adrenergic receptors and reduces plasma norepinephrine levels. It is not surprising therefore that the abnormalities described (sinus bradycardia, supraventricular pre-mature complexes, nonspecific intraventricular conduction delay and T-wave abnormalities) occur—none of which are harbingers of malignant arrhythmias. There have been three reports of sudden death in children taking methylphenidate and clonidine in combination from drug company surveillance information [80]. However in one child, no **clonidine** or **methylphenidate** was detected in the blood, in another child extensive pre-existing cardiac fibrosis was found and in the third, death followed a flu-like illness with headache and grand mal seizure. No other reports of QTc prolongation, cardiac arrhythmia or death with methylphenidate and/or **clonidine** were found. In a randomised trial of 136 children, the Tourette Study Group found no cardiac conduction abnormalities in children taking clonidine alone, methylphenidate alone or both together [2]. It is suggested that BP is measured prior to commencement and during discontinuation of **clonidine** as it can cause hypotension during treatment and rebound hypertension on discontinuation. ECG monitoring is not required for **clonidine** or **methylphenidate**.

In February 2006, the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) voted to recommend a "black-box" warning describing the cardiovascular risks of stimulant (amphetamines and methylphenidate) drugs used to treat ADHD. This was prompted by the frequency of prescription of these agents and their effects on heart rate and blood pressure [88].

Atomoxetine is a norepinephrine re-uptake inhibitor licensed for treatment of ADHD in children and adolescents. It has been shown to cause a small increase in heart rate and blood pressure at therapeutic doses, but has no significant effect on QTc interval [136, 137]. One case of prolonged QTc with an overdose of **atomoxetine** has been reported in a child co-medicated with bupropion, alprazolam and risperidone [108]. A report of 40 cases of atomoxetine overdose from a regional poisons centre noted no cases of QTc prolongation or arrhythmia [122].

A summary of suggested recommendations for ECG monitoring for some of the commonly used psychotropic drugs based on current evidence is shown in Table 3.

Clinical approach

Before prescribing a psychotropic medication in childhood, a detailed past medical and family history should be sought looking specifically for a family history of sudden death, a personal or family history of unexplained syncope or seizures, a history of congenital heart disease, deafness or disorders involving electrolyte imbalance, and use of medications that may cause electrolyte imbalance, interfere with metabolism of other medications or cause QT prolongation themselves. The purpose of this initial assessment is to ensure the absence of either a congenitally inherited or secondarily acquired predisposition to arrhythmia. As mentioned above, even medications that do not lead to QTc prolongation in the basal state may do so if a pre-existing risk factor is present. If the patient's history does not reveal any factors that may pre-dispose to arrhythmia, and the medication that is to be prescribed does not merit cardiovascular monitoring, no cardiac investigation is indicated. If the patient has a suspicious history or pre-existing risk factors, or is on medication that may

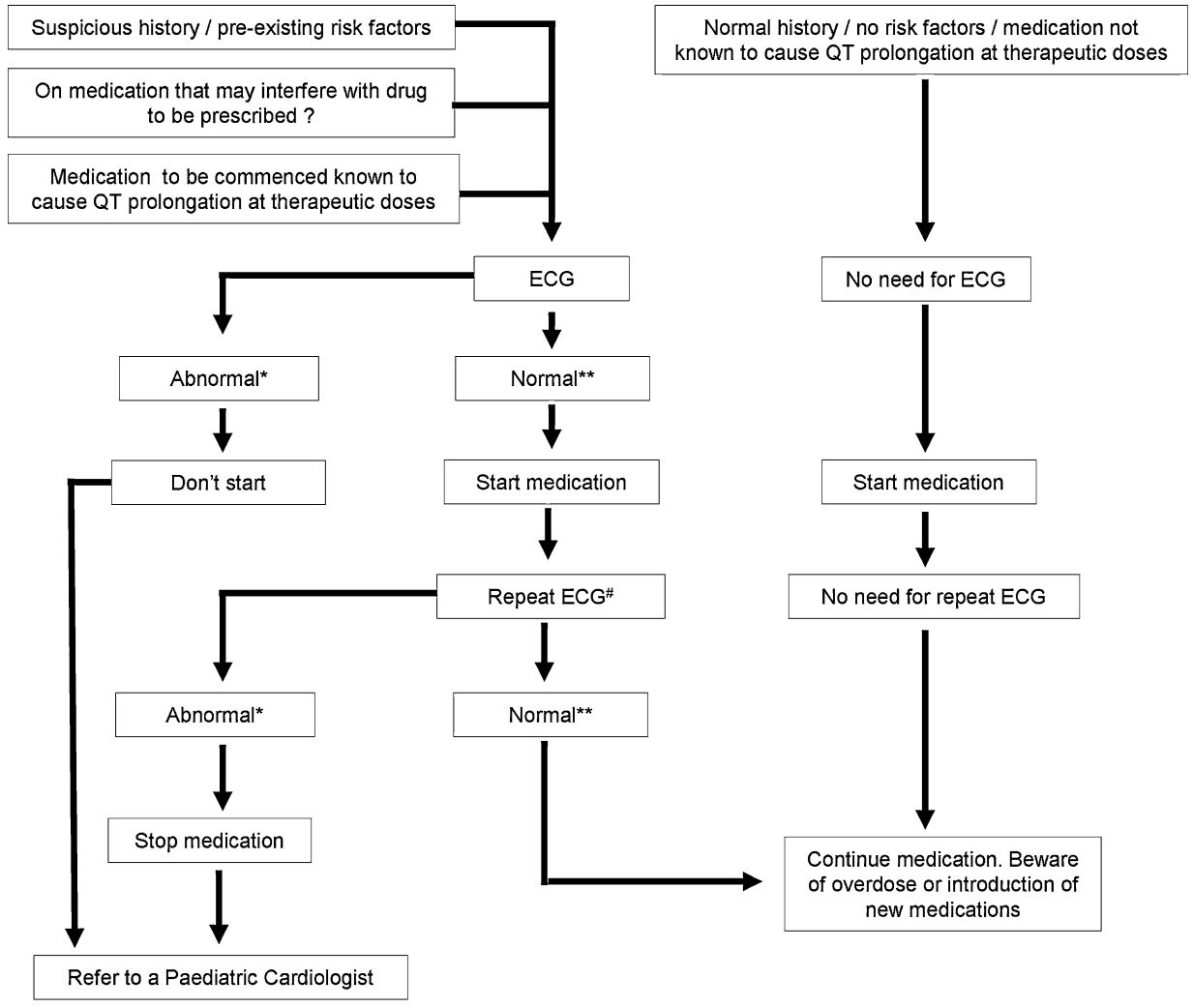
Table 3 Recommendations for ECG monitoring for some of the commonly used psychotropic drugs based on current evidence (March 2006). For up to date information on drug safety, see www.torsades.org

Drug	Summary of adverse effects reports	Monitoring reccomendations			
		Risk factors		No risk factors	
		ECG	F/U ECG	ECG	F/U ECG
Atypical antipsychotics					
Risperidone	Reports of mild QTcP in adults and in overdose. No cases of T de P	Yes	Yes	No	No
Comments	*Can produce mild QTcP of doubtful clinical significance. No reports of arrhythmias despite widespread use*				
Olanzapine	Case reports of QTcP in adults. No QTcP in overdose. No cases of T de P	Yes	Yes	No	No
Comments	*Can produce mild QTcP of doubtful clinical significance. No reports of arrhythmias linked to use*				
Quetiapine	Reports of QTcP in overdose only. No evidence for T de P	Yes	Yes	No	No
Comments	*Can produce mild QTcP of doubtful clinical significance. No evidence of link to arrhythmias*				
Ziprasidone	Reports of significant QTcP in children at therapeutic dose. No reports of T de P	Yes	Yes	Yes	Yes
Comments	*Causes more significant QTc prolongation than Risp, Olan and Quet. No reports of T de P, but has potential especially in OD*				
Aripiprazole	No QTcP in high dose animal studies, adults or children	No	No	No	No
Comments	*Seems very safe from cardiac viewpoint. Further vigilance required as new agent without extensive experience*				
Clozapine	Tachycardia, dose dependant QTcP at theraputic doses	Yes	Yes	Yes	Yes
Comments	*Can clearly cause QTcP at therapeutic doses. No reports of T de P clearly linked to use. Care needed, especially with co-medication*				
Typical antipsychotics					
Pimozide	Significant QTcP at theraputic doses	Yes	Yes	Yes	Yes
Comments	*Can clearly cause QTcP at therapeutic doses. Care needed, especially with co-medication*				
Haloperidol	Can Cause QTcP at thereutic doses and overdose. Many reports of T de P	Yes	Yes	Yes	Yes
Comments	*Can clearly cause QTcP at therapeutic doses. Care needed, especially with co-medication*				
Serotonin specific re-uptake inhibitors					
Fluoxetine	Isolated reports of QTcP at theraputic doses in adults.	Yes	Yes	No	No
Comments	*A widely used drug that is very safe on it's own but has significant potential to interact with other drugs*				
Citalopram	No QTcP at theraputic doses. QTcP prominent in overdose	Yes	Yes	No	No
Comments	*Does not cause QTcP at normal monotherapy doses. Beware combinations and overdose*				
Paroxetine	No QT prolongation in children on monotherapy. QTcP at theraputic doses in high risk adults	Yes	Yes	No	No
Comments	*Clinical experience with children has not shown effects on QTc*				
Sertraline	No QTcP at therapeutic doses. One report in combination overdose in adult. No T de P	Yes	Yes	No	No
Comments	*A very safe agent from cardiovascular viewpoint in children. Less potential for interaction than fluoxetine*				
Fluvoxamine	No significant QTcP either at therapeutic doses or in overdose. No T de P	Yes	Yes	No	No
Comments	*A very safe agent from cardiovascular viewpoint in children. Not as much experience as with other SSRIs*				
Newer antidepressants					
Venlafaxine	QTcP and arrhythmia reported in overdose. One adult report of QTcP at therapeutic doses	Yes	Yes	No	No
Comments	*Rare reports of cardiac toxicity especially in combination with other meds. Generally safe*				
Bupropion	QTcP common in overdose but not reported at therapeutic doses. No T de P	Yes	Yes	No	No
Comments	*Bupropion is very safe from a cardiac point of view. Only moderate QTcP in overdose—No T de P*				
Trazodone	QTcP and T de P in overdose. Arrhythmia at therapeutic doses with other medications	Yes	Yes	No	No
Comments	*Trazodone can be dangerous in overdose and in combination with other medications. Good safety profile with monotherapy*				
Drugs for ADHD					
Methylphenidate	No reports of QTcP. Can cause small increase in HR and BP	No	No	No	No
Comments	*Very safe. No need for cardiac monitoring*				
Clonidine	No reports of QTcP. Can cause hypotension and post-treatment rebound hypertension	No	No	No	No
Comments	*Very safe. Check BP prior to commencement and during discontinuation*				
Atomoxetine	Can cause small increase in HR and BP. One report of QTcP in overdose and co-medication	No	No	No	No
Comments	*Atomoxetine has consistently been shown to be safe from a cardiac conduction point of view.*				

F/U: Follow up QTcP: QTc prolongation: T de P: Torsades de Pointes HR: Heart rate BP: Blood pressure

interact with the medication to be prescribed, a baseline ECG is advised. In some cases, depending on the seriousness of the history, advice from a paediatric cardiologist may be required. A suggested algorithm for prescribing psychotropic medications in childhood is provided in Figure 4.

If the medication to be prescribed is documented to cause prolongation of the QTc interval at therapeutic



* QTc>450msec (males), >460msec (females, **QTc<450msec (males), <460msec (females), #ECG should be repeated when steady state drug level has been reached and with any subsequent significant dosage change

Fig. 4 Suggested algorithm for prescribing psychotropic medications in childhood

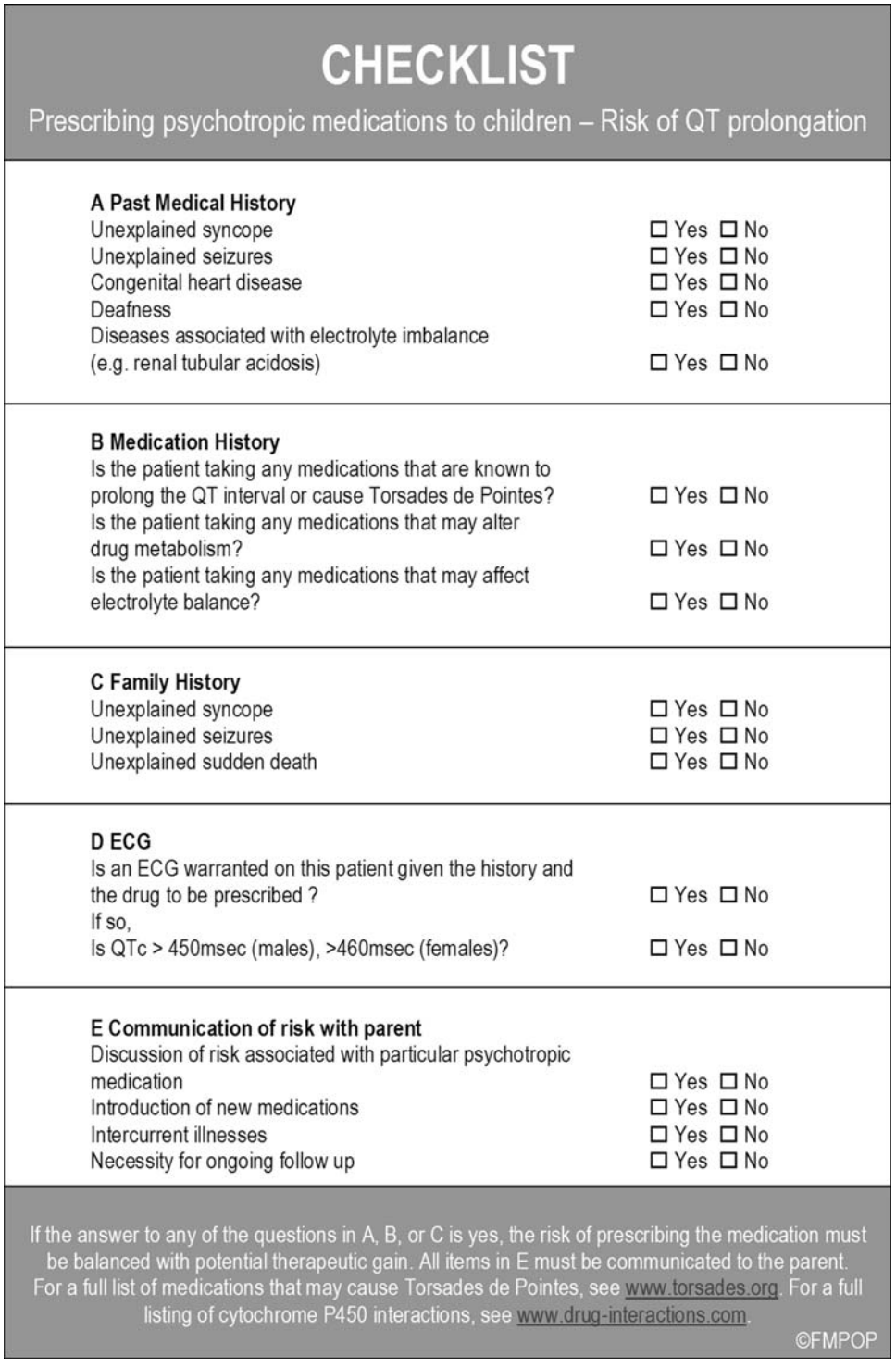
doses, a baseline ECG should be performed after a thorough history and examination. If this ECG shows a prolonged QTc interval, the child should be referred to a paediatric cardiologist. If the ECG is normal, it is advisable to repeat the ECG when a steady-state concentration of the drug has been reached and with any subsequent significant change in drug dosage.

Before prescribing a psychotropic medication to a child, the parent should be advised that the medication their child is taking may interact detrimentally with other medications. The parent should be aware that several antibiotics, other seemingly innocuous medications and even grapefruit juice may increase the blood level of their psychotropic medication. We would advise parents to contact the prescriber of the psychotropic medication if other doctors seek to prescribe additional medications for their children. Parents should also be warned about the dangers of excessive dehydration or other situations that may affect normal electrolyte balance.

Summary

The use of psychotropic medications in children has increased significantly in recent years. While most psychotropic medications, used at therapeutic doses, are safe, some have been linked with QTc prolongation. Several situations such as pre-existing risk factors, the addition of new medications and intercurrent illness can significantly increase the risk of malignant arrhythmia in children taking certain psychotropic medications. Clinicians prescribing psychotropic medications for children need to be aware of the risks involved with specific agents, and measures that can be taken to minimise these risks (Figs. 4, 5).

Fig. 5 Screening questionnaire



CHECKLIST

Prescribing psychotropic medications to children – Risk of QT prolongation

A Past Medical History

Unexplained syncope	☐ Yes ☐ No
Unexplained seizures	☐ Yes ☐ No
Congenital heart disease	☐ Yes ☐ No
Deafness	☐ Yes ☐ No
Diseases associated with electrolyte imbalance (e.g. renal tubular acidosis)	☐ Yes ☐ No

B Medication History

Is the patient taking any medications that are known to prolong the QT interval or cause Torsades de Pointes?	☐ Yes ☐ No
Is the patient taking any medications that may alter drug metabolism?	☐ Yes ☐ No
Is the patient taking any medications that may affect electrolyte balance?	☐ Yes ☐ No

C Family History

Unexplained syncope	☐ Yes ☐ No
Unexplained seizures	☐ Yes ☐ No
Unexplained sudden death	☐ Yes ☐ No

D ECG

Is an ECG warranted on this patient given the history and the drug to be prescribed ?	☐ Yes ☐ No
If so, Is QTc > 450msec (males), >460msec (females)?	☐ Yes ☐ No

E Communication of risk with parent

Discussion of risk associated with particular psychotropic medication	☐ Yes ☐ No
Introduction of new medications	☐ Yes ☐ No
Intercurrent illnesses	☐ Yes ☐ No
Necessity for ongoing follow up	☐ Yes ☐ No

If the answer to any of the questions in A, B, or C is yes, the risk of prescribing the medication must be balanced with potential therapeutic gain. All items in E must be communicated to the parent. For a full list of medications that may cause Torsades de Pointes, see www.torsades.org. For a full listing of cytochrome P450 interactions, see www.drug-interactions.com.

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