Effects of psychotropic medications on the pediatric electrocardiogram and recommendations for monitoring

Paul D. Francis, MD

Reports of sudden unexpected death in pediatric patients taking selected psychotropic drugs have raised the possibility of ventricular dysrhythmias as the cause of these deaths. The use of psychotropic drugs in the pediatric population has increased significantly in recent years with increasing reports of electrocardiogram abnormalities, particularly prolongation of the corrected QT interval. Many factors affect the susceptibility of the heart to conduction abnormalities and sudden ventricular dysrhythmias in pediatric patients taking psychotropic drugs. These complex relations include genetic predisposition, structural cardiac disease, drug-drug interactions, drug dosage, and drug metabolism and clearance. Many specific psychotropic drugs have been reported to prolong the QTc interval and increase the risk of ventricular dysrhythmias and sudden death. This article discusses the various factors that may influence the electrocardiogram in pediatric patients taking psychotropic drugs and recommendations for monitoring these patients. Curr Opin Pediatr 2002, 14:224–230

Department of Pediatrics, Janet Weis Children's Hospital, Geisinger Medical Center, Danville, Pennsylvania, USA.

Correspondence to Paul D. Francis, MD, Department of Pediatrics, Janet Weis Children's Hospital, Geisinger Medical Center, 100 N. Academy Ave., Danville, PA 17822, USA; e-mail: pfrancis@geisinger.edu

Current Opinion in Pediatrics 2002, 14:224–230

ISSN 1040–8703

The use of psychotropic drugs in the pediatric population has increased significantly in recent years [1•]. Reports of sudden, unexpected death in patients taking these drugs have raised the possibility of ventricular dysrhythmias as the cause of these deaths. Attention has centered on the electrocardiographic effects of psychotropic drugs. In addition, their interaction with other drugs metabolized by the cytochrome P450 (CYP450) system has come under scrutiny. Many psychotropic drugs affect electrolyte currents through ion channels. Myocardial repolarization is a function of ionic currents through these same channels. Alterations in sodium and potassium currents may prolong repolarization and increase the vulnerability of the myocardium to sudden ventricular dysrhythmias, particularly torsades de pointes. Effects on the electrocardiogram may be primarily significant or may be significant only in the presence of inherited or acquired predisposing factors. The Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young of the American Heart Association has published a statement for healthcare professionals concerning cardiovascular monitoring of children and adolescents receiving psychotropic drugs [2••]. It is important to understand the relation between the susceptibility of the heart to dysrhythmias and the use of psychotropic drugs. This article reviews various factors that may affect the electrocardiogram, the effects of specific psychotropic drugs on the electrocardiogram, and recommendations for electrocardiogram monitoring for patients on these drugs.

Factors that may increase susceptibility in patients taking psychotropic drugs

Genetic predisposition

Certain inherited congenital abnormalities of cardiac ionic channel function can lead to prolonged repolarization of the myocardium and can increase the risk of sudden dysrhythmias. This effect appears as a prolonged QTc interval on the electrocardiogram. The QTc is the measured QT interval corrected for heart rate. These inherited conditions include Romano-Ward syndrome (autosomal dominant) and Lange-Jervell-Nielsen syndrome (autosomal recessive with congenital hearing loss). Bradycardia, fright, loud noises, and exercise may provide settings particularly dangerous for patients with these syndromes. Other risk factors include serum electrolyte abnormalities; female gender; and renal, liver, or structural cardiac disease. Before instituting therapy with psychotropic drugs that may further prolong the QTc

interval, a detailed history should be obtained from the patient and family to document any history of palpitations, syncope, or near-syncope. A detailed family history should also be obtained. This family history should include inquiring about known relatives with prolonged QTc syndrome or the presence of sudden unexpected cardiac death, seizures, or syncope, especially in settings that may suggest an inherited prolonged QTc syndrome. Pharmacogenetics is an area of increasing interest, especially research concerning the existence of inheritable abnormalities of drug metabolism, which may predispose subpopulations to higher levels and effects of drugs metabolized by the CYP450 system. As much as 10% of the population may have impaired function of one or more of the isoenzymes of the CYP450 system. These poor metabolizers may have increased risk for proarrhythmia and sudden cardiac death [3••]. As identification of altered metabolism becomes clinically available, it may be possible to identify populations that are at increased risk. Until pharmacogenetic predisposition to drug effects is more fully elaborated, an accurate, detailed history and a screening baseline electrocardiogram are the only tools to evaluate for genetic susceptibility to drug effects and sudden cardiac death.

Structural cardiac disease

Underlying structural cardiac disease can predispose to heterogeneous ventricular depolarization and repolarization. Premature ventricular contractions are more common in patients with pre-existing heart disease. Preexisting heart disease increases the risk of ventricular dysrhythmias, which may trigger torsades de pointes in prolonged repolarization. Caution should be exercised when considering the use of psychotropic drugs that prolong the QTc interval or cause torsades de pointes in patients who have underlying structural heart disease.

Metabolism and clearance of psychotropic drugs and drug-drug interactions

Over 90% of drug oxidation and metabolism can be attributed to the cytochrome P450 enzyme system. Five isoenzymes are responsible for most of this metabolism: 3A4, 2D6, 1A2, 2C9, and 2C19. The 3A4 isoenzyme is involved in the widest range of drug metabolism, including liver and gut. Drugs that are substrates for a particular isoenzyme may competitively inhibit metabolism. Other drugs may directly inhibit isoenzyme function. Either of these effects may cause an increase in serum concentrations of psychotropic drugs with resultant risk of prolongation of the QTc interval and torsades de pointes.

Many psychotropic drugs cause little, if any, effect on the QTc interval at usual therapeutic dosages. However, at high therapeutic dosages or overdose, these same drugs may cause clinically significant QTc prolongation and lead to torsades de pointes because of inadequate clearance of the drug. It is important to assess the QTc interval if drug dosages change or if there is a clinically significant change in drug clearance, such as renal or hepatic dysfunction. Before starting psychotropic drugs, history and laboratory evidence of adequate hepatic and renal function should be ascertained. If changes in dosage are made, the hepatic and renal function should be addressed again. Also, if high dosages of drugs are used, additional surveillance of electrocardiogram changes should be undertaken. At follow-up visits, dosage changes or changes in renal or hepatic status should be explored.

Clinically significant drug-drug interactions exist. Many psychotropic drugs are metabolized through the CYP450 system. If the function of this enzyme system is inhibited directly or indirectly, elevated levels of drugs that effect cardiac repolarization may occur, with the potential for serious ventricular dysrhythmias. This is especially true of drugs primarily metabolized via the 3A4 isoenzyme of CYP450 [4]. Patients and families should be counseled about these possible interactions. Before starting new or additional medications, the physician or pharmacist should be queried concerning possible interactions with psychotropic drugs. This is especially true for drugs that are metabolized via CYP450 isoenzyme 3A4, such as macrolide antibiotics, and systemic antifungal medications. There are many cardiac medications that cause prolongation of the QTc interval, both as a specific therapeutic effect and as a side effect. Before adding any cardiac medication in a patient also taking psychotropic medications, specific attention to the potential for drug-drug interactions and QTc prolongation must be addressed.

Health care professionals should be cognizant of drug interactions that may alter drug metabolism and clearance. It is also imperative to warn patients and families about the potentially lethal consequences of using multiple drugs metabolized by the CYP450 system. Additions of new drugs, changes in clinical status, and changes in drug dosage should be considered in the decision about the use of psychotropic drugs and electrocardiographic monitoring (Tables 1 and 2).

Acute and chronic overdose

There are reports of electrocardiogram effects from psychotropic drugs in both acute and chronic overdose. Some drugs prolong the QTc interval in the therapeutic range but have not been reported to cause torsades de pointes in the literature or US Food and Drug Administration labeling. However, these drugs may cause clinically significant QTc prolongation in overdose. Clinicians should be aware of the possibility of significant electrocardiogram abnormalities and risk of dysrhythmias that may result from acute or chronic overdose of drugs that affect the QTc interval. Even drugs not recom-

Table 1. Drugs that induce QTc prolongation and/or torsades de pointes

QT prolongation	Torsades de pointes
	(Reported in the literature or in FDA labeling)
amiodarone	amiodarone*
arsenic trioxide	arsenic trioxide
bepridil	bepridil*
	chlorpromazine
cisapride	cisapride*††
	clarithromycin
desipramine	desipramine
disopyramide	disopyramide*
dofeltilide	dofeltilide
dolasetron	
	doxepin
droperidol	droperidol
erythromycin	erythromycin*
	felbamate
flecainide	flecainide
fluoxetine	fluoxetine
foscarnet	
fosphenytoin	
gatifloxacin	
halofantrine	halofantrine*
haloperidol	haloperidol
ibutilide	ibutilide*
imipramine	imipramine
indapamide	indapamide
isradipine	
	levofloxacin
levomethadyl	
mesoridiazine	mesoridiazine
moexipril	
moxifloxacin	
naratriptan	
nicardipine	
octreotide	
paroxetine	paroxetine
pentamidine	pentamidine*
pimozide	pimozide*
probucol	probucol*
procainamide	procainamide
	tacrolimus
quetiapine	
quinidine	quinidine*
risperidone	risperidone
salmeterol	
sertraline	sertraline
sotalol	sotalol*
tamoxifen	
terfenadine	terfenadine*†
sparfloxacin	sparfloxacin
sumatriptan	
thioridazine	thioridazine
tizanidine	
venlafaxine	
ziprasidone	
zolmitriptan	

*Females greater risk
††Restricted use
†Withdrawn from market

mended for routine electrocardiogram monitoring in therapeutic usage might have serious toxic effects in overdose. In acute or chronic overdose, electrocardiogram monitoring is essential. The clinician should also be aware that coingestion of other drugs in overdose that are metabolized by the CYP450 system might transform therapeutic levels of psychotropic drugs into toxic levels [4,5].

Specific psychotropic medications and recommendations for monitoring

Stimulants

Stimulants are the leading category of psychotropic medication prescribed for children (Table 3). Methylphenidate (Ritalin; Novartis Pharmaceutical Corp., East Hanover, NJ) is the most commonly prescribed medication for attention-deficit hyperactivity disorder. In addition, sustained-release methylphenidate (Concerta), pemoline (Cylert; Abbott Laboratories, Abbott Park, IL), and dextroamphetamine (Adderall; Richwood Pharmaceuticals, Florence, KY) are used. Underlying cardiac disorders such as supraventricular or ventricular tachydysrhythmias may be unmasked by stimulant medications. No specific electrocardiogram monitoring is recommended for stimulant monotherapy. There have been isolated reports of sudden death in children taking both methylphenidate and clonidine together. Although the exact mechanism remains unclear, it seems unlikely that these were dysrhythmic deaths [6,7]. No specific electrocardiogram monitoring is recommended [2••].

Antidepressants

Tricyclic antidepressants

Tricyclic antidepressants have been largely replaced by newer antidepressants, but they are still used in the treatment of depression and attention-deficit hyperactivity disorder. In addition, nocturnal enuresis and chronic pain are conditions for which tricyclic antidepressants are used. Several sudden deaths in children taking tricyclic antidepressants have been reported [8]. Nortriptyline, amitriptyline, desipramine, and imipramine may have significant cardiac effects with prolongation of the PR, QRS, and QTc intervals, even in therapeutic doses [9]. Significant drug-drug interactions exist. For example, methylphenidate may decrease metabolism, which may increase the concentration of tricyclic antidepressants. Synergism with other sympathomimetic drugs also occurs. The current recommendations include a careful history with a family history to screen for familial prolonged QTc syndrome. Medication history must be obtained to avoid drug-drug interactions. A baseline electrocardiogram should be obtained. Baseline electrocardiogram measurements should include a PR interval $\leq$ 200 ms, a QRS duration $\leq$ 120 ms, and a QTc $\leq$ 460 ms. Follow-up electrocardiograms should be obtained after a steady state is established to ascertain that the electrocardiogram intervals remain in the acceptable range [2••].

Selective serotonin reuptake inhibitors

Fluoxetine (Prozac; Eli Lilly & Co., Indianapolis, IN), citalopram (Celexa; Forest Pharmaceutical, St. Louis, MO), sertraline (Zoloft; Roerig, New York, NY), fluvoxamine (Fluvox), and paroxetine (Paxil; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) are commonly used selective serotonin reuptake inhibitor anti-

Table 2. Cytochrome P 450 isoenzyme function

Substrates*					
1A2					
clozapine	cyclobenzapine	imipramine	mexillitine	naproxen	niluzole
tacrine	theophylline				
2C19					
omeprazole	diazepam	amitriptyline	progesterone		
lansoprazole	phenytoin	clomipramine			
pantoprazole	phenobarbital	cyclophosphamide			
2C9					
diclofenac	tolbutamide	irbesartan	naproxen	tamoxifen	toresimide
ibuprofen	glipizide	celecoxib	phenytoin	tolbutamide	warfarin
piroxicam	losartan	fluvastatin	sulfamethoxazole		
2D6					
metoprolol	amitriptyline	haloperidol	codeine	dextromethoraphan	
propafenone	clomipramine	risperidone	flecainide	venlafaxine	
timolol	desipramine	thioridazine	tamoxifen		
	imipramine		ondansetron		
	parxetine		tramadol		
2E1					
acetaminophen					
chlorzoxazone					
ethanol					
3A4					
clariththromycin	alprazolam	cyclosporine	indinavir	astemizole	
erythromycin	diazepam	tacrolimus	ritonavir	chlorpheniramine	
quinidine	midazolam	atorvastatin	saquinavir	amlodipine	
buspirone	triazolam	cerivastatin	pimozide	diltiazem	
haloperidol	methadone	lovastatin	quinine	felodipine	
sildenafil	tamoxifen	trazodone	vincristine	nifedipine	
				nisoldipine	
				nitrendipine	
				verapamil	
Inhibitors†					
1A2					
cimetidine					
fluoroquinolones					
fluvoxamine					
ticlodipine					
2C19					
fluoxetine	lansoprazole				
fluvoxamine	omeprazole				
ketoconazole	ticlodipine				
2C9					
amiodarone	ticlodipine				
fluconazole					
isoniazid					
2D6					
amiodarone	chloripramine	methadone	quinidine		
bupropion	fluoxetine	mibefradil	ritonavir		
chlorpheniramine	haloperidol	paroxetine			
cimetidine					
2E1					
disulfram					
3A4					
indinavir	amiodarone	fluoxetine	ketoconazole		
nelfinavir	cimetidine	fluvoxamine	mibefradil		
ritonavir	clarithromycin	grapefruit juice	nefazodone		
saquinavir	erythromycin	itraconazole	troleandomy		

*Simultaneous use of drugs that are substrates for the CTP 450 system may lead to competitive inhibition and altered levels of drugs and active metabolites. ECG monitoring is recommended when these drugs are used in combination with drugs known to prolong the QTc.
†The simultaneous use of drugs that alter cytochrome P 450 function may alter drug and active metabolite levels. ECG monitoring is recommended when these drugs are used in combination with drugs known to prolong the QTc.

depressants. Fluoxetine has been reported to prolong the QTc interval, which causes syncope [10]. Citalopram has been reported to show no significant effects on cardiac intervals in therapeutic usage but may prolong the QTc in overdose [11]. Paroxetine has been shown to lengthen the QTc interval, and the Food and Drug Administration labeling mentions torsades de pointes [12]. The different selective serotonin reuptake inhibitors are metabolized by different cytochrome P450 enzymes, and potential interactions with other drugs that share the same metabolism should be monitored [13•]. Although no consensus has been established, baseline electrocardiogram measurements may be considered before instituting selective serotonin reuptake inhibitor therapy. Baseline

Table 3. Electro-cardiogram monitoring recommendations

Category 1–Baseline and Periodic ECG monitoring recommended:
Tricyclic antidepressants
Desipramine
Doxepin
Imipramine
Nortryptilline
Phenothiazines
Chlorpromazine
Fluphenazine
Mesoridazine
Perphenazine
Thioridazine
Trifluoperazine
Butyrophenones
Droperidol
Haloperidol
Atypical Neuroleptics
Pimozide
Category 2–Baseline ECG recommended:
Anticonvulsants
Felbamate
Atypical neuroleptics
Olanzapine
Quetiapine
Risperidone
Selective serotonin reuptake inhibitors
Fluoxetine
Paroxetine
Sertraline

ECG, electrocardiogram.
Category 1 drugs require baseline ECG documenting PR interval ≤200 msec, QRS interval ≤120 msec and QTc ≤460. Follow up ECG required when steady state achieved documenting ECG intervals remain in the acceptable range.
Category 2 drugs require baseline ECG documenting PR interval ≤200 msec, QRS interval ≤120 msec and QTc ≤460. No follow up EKG's recommended unless toxicity suspected or symptoms of palpitations, syncope or near-syncope develop.
If additional drugs are added that can cause QTc prolongation or that alter the function of the CYP 450 system, then a repeat ECG is indicated.

electrocardiogram measurements should include a PR interval ≤ 200 ms, a QRS duration ≤ 120 ms, and a QTc ≤ 460 ms. Electrocardiogram monitoring is indicated in proven or suspected overdose.

Newer antidepressants

Bupropion (Wellbutrin; GlaxoWellcome, Research Triangle Park, NC) increases dopamine reuptake and has minor effects on norepinephrine reuptake. Bupropion is metabolized by the 2B6 isoenzyme of the CYP450 system and can inhibit the 2D6 isoenzyme. No change in the QTc has been reported with bupropion, but caution should be exercised when using other drugs metabolized by the CYP450 system. Venlafaxine (Effexor; Wyeth-Ayerst Laboratories, Philadelphia, PA) inhibits the reuptake of serotonin and norepinephrine. At high doses, it also inhibits the reuptake of dopamine. Venlafaxine has been shown to cause prolongation of the QTc interval in overdose but not at therapeutic levels. Trazodone (Desyrel; Bristol-Myers Squibb, Princeton, NJ), nefazodone (Serzone; Bristol-Myers Squibb, Princeton, NJ), and mirtazepine (Remeron; Organon Teknika Corp., Durham, NC) do not prolong the QTc interval in therapeutic usage. There have been reports of trazodone and nefazodone causing QTc prolongation in overdose [14].

Mood stabilizers

Mood stabilizers are used mainly to treat manic-depressive disorders. Lithium and valproic acid (Depokote, Abbott Laboratories, Abbott Park, IL) are the two major drugs in this category. However, it should be noted that the novel antiepileptic drugs are potential mood stabilizers, and their use may increase in the future. Newer anticonvulsants such as gabapentin (Neurontin; Parke-Davis, Morris Plains, NJ), topiramate (Topamax; Ortho McNeil Pharmaceutical, Raritan, NJ), and lamotrigine (Lamictal; GlaxoWellcome, Research Triangle Park, NC) have been tried as mood stabilizers in the treatment of attention-deficit hyperactivity disorder [15••]. None of these drugs is reported to cause prolongation of the QTc interval. Although lithium does cause T-wave flattening but not QTc prolongation in therapeutic usage, it has rarely been reported to cause arrhythmias in overdose. Lithium has been reported to cause QTc prolongation in chronic toxicity. Lithium levels may be increased by diuretics, especially thiazide diuretics. For drugs in this category, no specific electrocardiogram monitoring is indicated at therapeutic levels. However, in the setting of acute or chronic toxicity, electrocardiogram monitoring is indicated.

α-Adrenergic agents

Clonidine (Catapres; Boehringer Ingelheim, Ridgefield, CT) and Guanfacine (Tenex; Wyeth-Ayerst Laboratories, Philadelphia, PA) are α-2 adrenergic agonists, that lower blood pressure. No electrocardiogram changes have been reported. Blood pressure should be monitored at the institution of therapy and at the time of weaning. No electrocardiogram monitoring is indicated [2••].

Typical antipsychotics and neuroleptics

Phenothiazines

Chlorpromazine (Thorazine; SmithKline Beecham Pharmaceuticals, Philadelphia, PA), thioridazine (Mellaril; Novartis Pharmaceutical Corp., East Hanover, NJ), mesoridazine (Serentil; Boehringer Ingelheim, Ridgefield, CT), perphenazine (Trilafon; Schering-Plough Corp., Kenilworth, NJ), trifluoperazine (Stelazine; SmithKline Beecham Pharmaceuticals, Philadelphia, PA), and fluphenazine (Prolixin; Bristol-Myers Squibb, Princeton, NJ) may cause hypotension or tachycardia from anticholinergic effects. Chlorpromazine may affect the fast sodium channel with a quinidine-like effect. Phenothiazines have been shown to cause QTc prolongation and may predispose to broad complex tachycardia, ventricular tachycardia, or torsades de pointes [16•,17•]. The current recommendations include a careful history with a family history to screen for familial prolonged QTc syndrome. Medication history must be obtained to avoid drug-drug interactions. A baseline electrocardiogram

should be obtained. Baseline electrocardiogram measurements should include a PR interval ≤ 200 ms, a QRS duration ≤ 120 ms, and a QTc ≤ 460 ms. Follow-up electrocardiograms should be obtained after a steady state is established to ascertain that the electrocardiogram intervals remain in the acceptable range [2••].

Acute overdose with phenothiazines is associated with supraventricular tachydysrhythmias and ventricular tachycardia, including torsades de pointes. Mesoridazine and thioridazine are considered the most cardiotoxic of the phenothiazines in overdose. Electrocardiogram monitoring is imperative in the pediatric patient with suspected acute or chronic toxicity.

Butyrophenones

Haloperidol (Haldol; Ortho McNeil Pharmaceutical, Raritan, NJ) and droperidol (Inapsine; Janssen Pharmaceutical, Titusville, NJ) are the two most common butyrophenones. They may cause tachycardia from anticholinergic effects. Haloperidol and droperidol have been demonstrated to be antagonists of the potassium channel. Both haloperidol and droperidol have been shown to cause QTc prolongation and may predispose to ventricular tachycardia or torsades de pointes [18,19]. The current recommendations include a careful history with a family history to screen for familial prolonged QTc syndrome. Medication history must be obtained to avoid drug-drug interactions. A baseline electrocardiogram should be obtained. Baseline electrocardiogram measurements should include a PR interval less than 200 ms, a QRS duration less than 120 ms, and a QTc ≤ 460 ms. Follow-up electrocardiograms should be obtained after a steady state is established to ascertain that the electrocardiogram intervals remain in the acceptable range [2••].

Diphenylbutylpiperidine

Pimozide (Orap; Ortho McNeil Pharmaceutical, Raritan, NJ) is the prototypical diphenylbutylpiperidine. Pimozide is used in the treatment of Tourette syndrome. The drug has dopaminergic receptor blockade effects, but the exact mechanism of action has not been fully delineated. Pimozide has been shown to cause significant QTc prolongation [20•]. The current recommendations include a careful history with a family history to screen for familial prolonged QTc syndrome. Medication history must be obtained to avoid drug-drug interactions. A baseline electrocardiogram should be obtained. Baseline electrocardiogram measurements should include a PR interval ≤ 200 ms, a QRS duration less than 120 ms, and a QTc less than 460 ms. Follow-up electrocardiograms should be obtained after a steady state is established to ascertain that the electrocardiogram intervals remain in the acceptable range [2••].

Atypical antipsychotics and neuroleptics

Olanzapine (Zyprexa; Eli Lilly & Co., Indianapolis, IN), risperidone (Risperidal; Janssen Pharmaceutical, Titusville, NJ), quetiapine (Seroquel; Zeneca Pharmaceuticals, Wilmington, DE), and ziprasidone (Geodon) are classified as atypical neuroleptics. Atypical neuroleptics have replaced traditional neuroleptics because they have fewer side effects. These agents affect dopamine, serotonin, muscarinic, α-2 adrenergic, and histamine receptors. Olanzapine and risperidone have some prolongation of the QTc in experimental models [19,21]. A cardiac fatality on initiation of risperidone therapy has been reported [22]. Ziprasidone has also been shown to prolong the QTc. In acute quetiapine poisoning, QTc prolongation has been reported [23]. Olanzapine has not been shown to have significant QTc prolongation in therapeutic use [20•]. For olanzapine, quetiapine, ziprasidone, and Risperdal (Janssen Pharmaceutical, Titusville, NJ), a baseline electrocardiogram should be obtained before initiating medication [15••,24,25•,26•,27••]. Baseline electrocardiogram measurements should include a PR interval less than 200 ms, a QRS duration less than 120 ms, and a QTc less than 460 ms. Follow-up electrocardiograms should be obtained after a steady state is established to ascertain that the electrocardiogram intervals remain in the acceptable range. In acute or chronic overdose, additional electrocardiogram monitoring is indicated. Molindone (Moban; Du Pont Merck Pharmaceutical Co., Wilmington, DE) is another atypical neuroleptic. Molindone has not been reported to prolong the QTc, and no specific cardiac monitoring is recommended [2••].

General recommendations for determining risk for potential electrocardiogram abnormalities

- History: document any past history of syncope, near syncope, or palpitations; ascertain family history of deafness, sudden unexpected cardiac death, syncope, or tachydysrhythmias; obtain medication history to document all medications that may have direct or indirect effects on the CYP450 system or electrocardiogram intervals
- Physical examination: document presence or absence of normal cardiovascular exam; check vital signs, including blood pressure and heart rate
- Baseline electrocardiogram: obtain baseline electrocardiograms in patients starting drugs known to affect the QTc interval at therapeutic levels or reported to cause torsades de pointes in the literature (Table 1)
- Follow-up electrocardiogram: obtain follow-up electrocardiograms for drugs known to cause torsades de pointes after therapeutic steady state is established

Follow-up evaluations: inquire about new medications, change in dosage, new symptoms, and changes or possible changes in hepatic or renal function

Other drugs: counsel patient and family about the effects of drugs on the cytochrome P450 system; avoid other drugs that increase the QTc or cause torsades de pointes (Table 2) [2••,28•].

Conclusions

Psychotropic drugs are used in a wide variety of clinical settings. Ventricular dysrhythmias are an unusual but potentially life-threatening side effect of these drugs. Multiple factors affect concentration of psychotropic drugs and vulnerability to dysrhythmias. These factors include dosage, genetic predisposition, drug-drug interactions, clearance, and metabolism. It is imperative that patients, families, and health care professionals understand these potentially lethal interactions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 Zito JM, Safer DJ, dosReis S, et al.: Trends in the prescribing of psychotropic
• medications to preschoolers. JAMA 2000, 283:1025–1030.
Illustrates the magnitude of the problem in pediatrics with increasing use of psychotropic drugs.

2 Gutgesell H, Atkins D, Barst R, et al.: Cardiovascular monitoring of children
•• and adolescents receiving psychotropic drugs. Circulation 1999, 99:979–982.
Statement for healthcare professionals with practical recommendations.

3 Idle J: [letter]. Lancet 2000, 355:1824.
••
Brief communication concerning the future of pharmacogenetics and the possibility of genetic screening for drug susceptibility in the future. Raises very interesting issues.

4 Shapiro L, Shear N: Drug-drug interactions: how scared should we be? CMAJ 1999, 161:1266–1267.

5 Michalets E: Update: clinically significant cytochrome P 450 drug interactions. Pharmacotherapy 1998, 18:84–112.

6 Dech B: Conidine and Methylphenidate [letter]. J Am Acad Child Adolesc Psychiatry 1999, 38:1469–1470.

7 Wilens T, Spencer T, Swanson J, et al.: Combining methylphenidate and clonidine: a clinically sound medication option. J Amer Acad Child Adolesc Psychiatry 1999, 38:614–619.

8 Popper C, Zimnitzky B: Sudden-death putatively related to desipramine treatment in youth: a fifth case and a review of speculative mechanisms. J Child Adolesc Psychopharmacol 1995, 5:283–300.

9 Wilens T, Biederman J, Baldessarini R, et al.: Cardiovascular Effects of therapeutic doses of tricyclic antidepressants in children and adolescents. J Am Acad Child Adolesc Psychiatry 1996, 35:1491–1501.

10 Ravina T, Suarez ML, Mendez-Castrillon J: Fluoxetine-induced QTU prolongation, T wave alternans and syncope. Int J Cardiol 1998, 65:311–313.

11 Rasmussen S, Overko K, Tanghoj P: Cardiac safety of citalopram: prospective trials and retrospective analysis. J Clin Psychopharmacol 1999, 19:407–415.

12 Erluth A, Loew M, Dobmeier P, et al.: [ECG changes after paroxetine: 3 case reports] [German]. Nervenarzt 1998, 69:629–631.

13 Yergani V, Pohl R, Jampala V: Effects of nortriptyline and paroxetine on QT
• variability in patients with panic disorder. Depression Anxiety 2000, 11:126–130.
Clinical study showing less QT variability and greater safety of paroxetine.

14 Levinson J: Prolonged QT interval after trazodone overdose. Am J Psychiatry 1999, 156:969–970.

15 Jacobs E, Dickstein D, Liebelt E: Novel psychotropic medications in children:
•• new toxicities to master. Pediatr Emerg Care 2001, 17:226–231.
Excellent review of newer psychotropic medications. Good discussion of toxicities. However, pimozide is not discussed.

16 Dallaire S: Thioridazine (Mellaril) and mesoridazine (Serentil) prolongation of
• the QTc interval. CMAJ 2001, 164:91–95.
Clinical study confirming QTc prolongation of phenothiazines.

17 Reilly JG, Ayis SA, Ferrier IN, et al.: QTc-interval abnormalities and psycho-
• tropic drug therapy in psychiatric patients. Lancet 2000, 355:1048–1052.
This clinical study found that tricyclic antidepressants, droperidol, and thioridazine had significant QTc prolongation but not increased QT variability or T-wave abnormalities.

18 O'Brien J, Rockwood R, Suh K: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999, 33:1046–1050.

19 Drici M, Wang W, Liu X, et al.: Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol 1998, 18:477–481.

20 Welch R, Chue P: Antipsychotic agents and QT changes. J Psychiatry Neu-
• rosci 2000, 25:154–160.
Basic science research identifying the ionic channels effected by a variety of antipsychotic drugs.

21 Shen W: The metabolism of atypical antipsychotic drugs: an update. Ann Clin Psychiatry 1999, 11:145–158.

22 Ravin D, Levenson J: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997, 31:867–870.

23 Hustey F: Acute quetiapine poisoning. J Emerg Med 1999, 17:995–997.

24 Accri A, Henretig F: Effects of risperidone in overdose. Am J Emerg Med 1998, 16:498–501.

25 Czekella J, Beasley C, Dellva M, et al.: Analysis of the QTc interval during
• olanzapine treatment of patients with schizophrenia and related psychoses. J Clin Psychiatry 2001, 62:191–198.
Clinical article on the safety of olanzapine.

26 Gury C, Canceil C, Iaria P: [Antipsychotic drugs and cardiovascular safety:
• current studies of prolonged QT interval and risk of ventricular arrhythmia] [French]. Encephale 2000, 26:62–72.
Comparison of the effects and potential risk of several newer antipsychotic drugs.

27 Woosley R: Drugs that prolong the QT interval and/or induce torsades de
•• pointes. Available at: http://georgetowncert.org/qtdrugs_torsades.asp.
Excellent reference Web site for current information on drugs that prolong the QTc interval or that have been reported to cause torsades de pointes.

28 Havercamp W, Breithardt G, Camm A, et al.: The potential for QT prolonga-
• tion and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications: report on a policy conference of the European Society of Cardiology. Eur Heart J 2000, 21:1216–1231.
Exhaustive report on drugs that may prolong the QTc interval. Governmental and regulatory issues are discussed.