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REVIEW ARTICLE

F. De Ponti · E. Poluzzi · N. Montanaro

QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience

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Abstract *Background*: Evidence has accrued that several non-cardiac drugs may prolong cardiac repolarisation (hence, the QT interval of the surface electrocardiogram) to such a degree that potentially life-threatening ventricular arrhythmias (e.g. torsades de pointes) may occur, especially in case of overdosage or pharmacokinetic interactions.
Discussion: This has fostered discussion on the molecular mechanisms underlying the class-III antiarrhythmic effect shared by apparently disparate classes of drugs, on the clinical relevance of this side effect and on possible guidelines to be followed by drug companies, ethics committees and regulatory agencies in the risk–benefit assessment of new and licensed drugs. This review provides an update on the different classes of non-cardiac drugs reported to prolong the QT interval (e.g. histamine H_1-receptor antagonists, antipsychotics, antidepressants and macrolides), on the possible underlying molecular mechanisms and on the clinical relevance of the QT prolonging effect. Identification and widespread knowledge of risk factors that may precipitate prolongation of the QT interval into life-threatening arrhythmias becomes an important issue. Risk factors include congenital long QT syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (especially hypokalaemia, hypomagnesaemia), impaired hepatic/renal function and concomitant treatment with other drugs with known potential for pharmacokinetic/pharmacodynamic interactions (e.g. azole antifungals, macrolide antibacterials and class-I or -III antiarrhythmic agents). Future perspectives for drug research and development are also briefly outlined.

F. De Ponti (✉) · E. Poluzzi · N. Montanaro
Department of Pharmacology,
University of Bologna and Interuniversity Research Centre
for Pharmacoepidemiology, Via Irnerio 48,
I-40126 Bologna BO, Italy
e-mail: deponti@biocfarm.unibo.it
Tel.: +39-051-2091805; Fax: +39-051-248862

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Introduction

Since the mid 1980s, evidence has accrued that several classes of non-cardiac drugs may significantly prolong the QT interval of the surface electrocardiogram (ECG) and have cardiotoxic potential (risk of life-threatening arrhythmias). In the 1960s and 1970s, reports already existed on the cardiotoxicity of some drug classes, such as anti-psychotics and first-generation histamine H_1-receptor antagonists (for references, see Zhang [1] and Kitayama et al. [2]), but these remained mostly confined to the specialised literature, and the ability of non-cardiac drugs to prolong the QT interval was usually considered as a pharmacological ''curiosity'' of uncertain clinical significance and the molecular mechanisms remained obscure.

Several reasons have fuelled interest on the QT-prolonging potential of non-cardiac drugs. Firstly, drug-induced lengthening of the QT interval (stemming from a drug's ability to prolong the cardiac action potential duration) has been associated with the occurrence of ventricular tachyarrhythmias, namely *torsades de pointes*, a polymorphous ventricular arrhythmia that may cause syncope and degenerate into ventricular fibrillation [3]. Secondly, there is an ongoing debate in the literature [4] on the clinical significance of a prolonged QT interval, which has been found to be a risk factor for sudden death due to cardiac arrest [5] and also for all-cause mortality [6, 7]. Thirdly, several apparently chemically unrelated classes of drugs have been implicated in prolongation of the QT interval, and pharmacologists have been challenged by the question whether this is a class effect (e.g. shared by all agents of a given pharmacological class such as antihistamines) or a specific effect of a few agents within a pharmacological class. Finally, several interventions by regulatory agencies and/or drug companies (Table 1) have fostered

Table 1 Examples of interventions on non-cardiac drugs with QT prolonging potential

	USA	Europe
Terodiline	–	Withdrawn after reports of cases of torsades de pointes (1991)
Terfenadine	Proposal to withdraw (January 1997)[a] Drug labelling changes: new warnings (September 1997)[b] Withdrawn after approval of fexofenadine (December 1997)[c]	120-mg Tablets withdrawn from EU market (November 1997)[d] 60-mg and 30-mg tablets and 6-mg/ml oral suspension maintained (February 1998)[e]
Cisapride	Drug labelling change: new warnings (1998)[f]	Drug labelling change: new warnings (1998)[g]
Sertindole	Recommended for approval, but not licensed (1996)[h]	Precautionally withdrawn from EU market pending EMEA judgement (1998)[i]
Astemizole	Withdrawn by the manufacturer (1999)	Withdrawn by the manufacturer (1999)
Grepafloxacin	Withdrawn by the manufacturer (1999)	Withdrawn by the manufacturer (1999)

[a] http://www.fda.gov/medwatch/safety/1997/seldan.htm
[b] http://www.fda.gov/bbs/topics/ANSWERS/ANS00823.html
[c] http://www.fda.gov/bbs/topics/ANSWERS/ANS00843.html
[d] http://www.eudra.org/humandocs/PDFs/PhV/EN/100097en.pdf
[e] http://www.eudra.org/humandocs/PDFs/PhV/EN/025598en.pdf; http://www.eudra.org/humandocs/PDFs/PhV/EN/025698en.pdf; http://www.eudra.org/humandocs/PDFs/PhV/EN/025798en.pdf
[f] http://www.fda.gov/medwatch/safety/1998/propul.htm
[g] http://www.imb.ie/pubs/drugnews/news8.pdf
[h] http://www.fda.gov/oc/oms/ofm/budget/fooddrugstat.htm; http://www.fda.gov/cder/da/da1096.htm
[i] http://www.open.gov.uk/mca/csm/serdolect.htm

discussion on the impact of QT-prolonging effects on drug development and on whether a more carefully focussed drug-development program could have prevented some of the reported fatal adverse reaction. This dilemma is not easily solved, since, although prolongation of the QT interval by non-cardiac drugs is not an unusual finding, potentially fatal arrhythmias, such as torsades de pointes, are uncommon and are unlikely to occur during the course of phase I–III studies, when relatively small numbers of subjects are exposed to the investigational drug. However, when we analyse some of the initial case reports of drug-induced life-threatening arrhythmias with hindsight, it is clear that several of these adverse reactions would have been preventable, had the potential for pharmacokinetic interactions (e.g. with CYP3A4 isoenzyme inhibitors) been known at that time.

The aim of this review is to provide an updated overview of different classes of compounds that are not intended for cardiac use and have been reported to prolong the QT interval, to outline possible pharmacodynamic/pharmacokinetic mechanisms and to consider this information from a clinical and regulatory perspective.

Classes of drugs and mechanisms underlying QT prolongation

Through a Medline search for literature published from 1985 through 1998 using the MESH terms "long-QT syndrome – chemically induced" or "torsades-de-pointes – chemically induced", we retrieved 391 records. This approach was used as a starting point to obtain an overview of the drugs associated with a prolonged QT interval (Fig. 1), although it certainly underestimates the real number of publications dealing with drug-induced prolongation of the QT interval. The 391 Medline records were classified as indicated in Fig. 1, and the 197 case reports/case series (for a total number of 236 cases) were analysed by identifying the drugs/drug classes associated with prolongation of the QT interval/occurrence of torsades de pointes. Apart from anti-arrhythmics, the largest numbers of cases within single classes refer to anti-psychotics, histamine H_1-receptor antagonists and macrolides.

With such a diverse spectrum of molecules, the pharmacologist is challenged by questions on the molecular mechanism(s) underlying prolongation of the QT interval by apparently unrelated molecules. Table 2 provides a synopsis of different classes of drugs with QT-prolonging potential and possible mechanisms of class-III anti-arrhythmic action.

Since the QT interval is the summation of the duration of ventricular depolarisation and repolarisation, it is thought to reflect individual action potential duration in cardiac myocytes. Cardiac action potential duration is in turn controlled by a delicate balance between inward and outward currents in the plateau repolarisation phase. Since outward K^+ currents, especially the delayed rectifier repolarising current, I_K (which is the sum of two kinetically and pharmacologically distinct types of K^+ currents: a rapid I_{Kr} and a slow I_{Ks} component), are thought to play an important role during plateau repolarisation and in determining the configuration of the action potential, small changes in conductance can significantly alter the effective refractory period, hence the action potential duration.

Several studies support the notion that the basic mechanism by which most of the drugs listed in Table 2 prolong the QT interval can be related to blockade of potassium currents. Drugs such as amiodarone and d-sotalol exert their class-III anti-arrhythmic properties through this mechanism. In particular, d-sotalol fully blocks the rapid component of I_K (I_{Kr}) at concentrations that have no effect on I_{Ks}. Several of the drugs

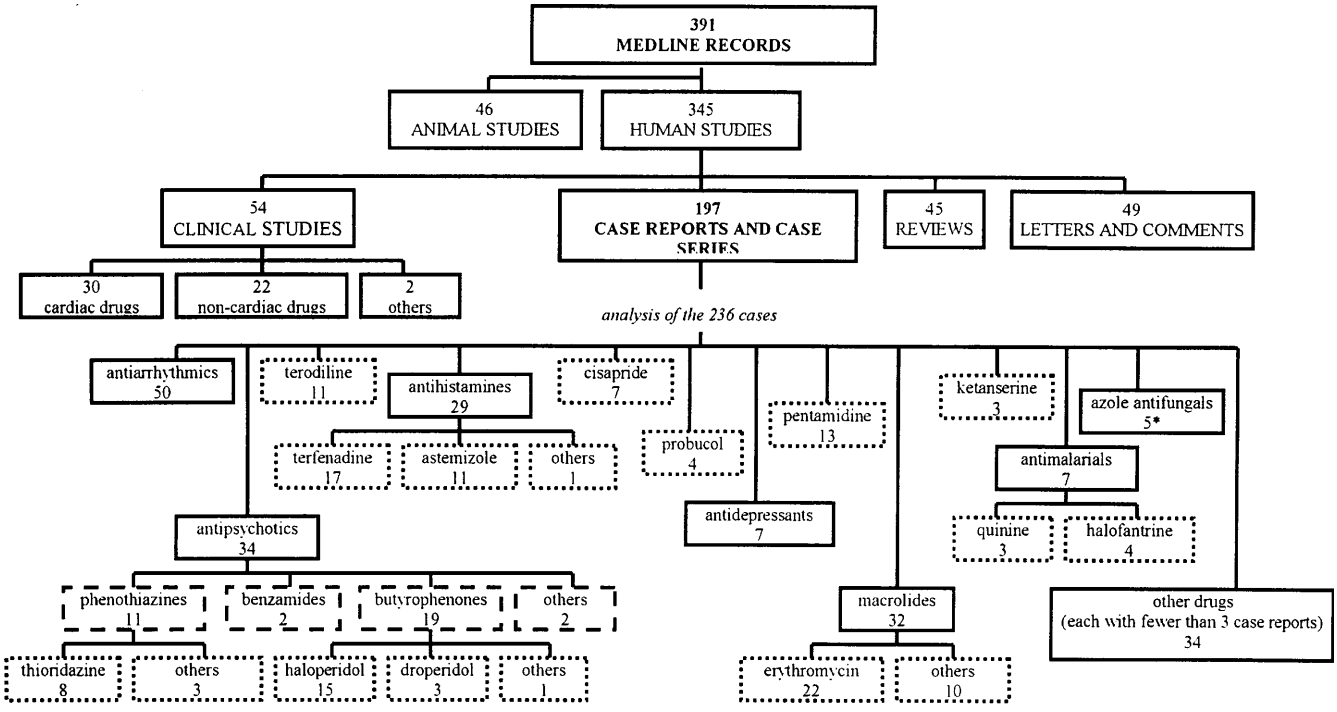

Fig. 1 Records obtained through a Medline search for literature published from 1985 to 1998, using the MESH terms "long-QT-syndrome – chemically-induced" or "torsades-de-pointes – chemically induced". The search retrieved 391 records: 345 refer to humans and 197 are case reports or case series. The latter include a total number of 236 cases, which were analysed by identifying the compounds associated with prolongation of the QT interval/occurrence of torsades de pointes. *Numbers* below a drug/drug class refer to the number of the reported cases

reported to significantly prolong the QT interval in a clinical setting (such as terfenadine, astemizole and i.v. macrolides) were shown to inhibit the rapid component of the delayed rectifier K^+ current (I_{Kr}) in electrophysiological studies and to block potassium channels encoded by the human ether-à-go-go-related gene (HERG) (see Table 2 and Table 3 for references). Although I_{Kr} is the most extensively studied, action on other potassium currents (e.g. the transient outward current I_{to}, the ultrarapidly activating delayed rectifier current I_{Kur} and the inward rectifier I_{K1} current) may account for a prolongation of the action potential duration. Several reviews on cardiac potassium channels and on gene(s)/gene product(s) thought to be responsible for a given current are available [8, 9, 10]. At present, the role of different currents in shaping the cardiac action potential in health and disease is a matter of extensive investigations, and the clinical application of basic knowledge on ionic currents is still in its infancy. The overall relevance of a given current may depend on the type of ion channels expressed in different parts of the heart (e.g. atrium vs ventricle), on the species and on the pathophysiological condition (low vs high heart rate; ischaemic vs normal myocardium).

Structure–activity relationships for QT-prolonging effect

It may seem surprising that, at present, our knowledge on structure–activity relationships for class-III anti-arrhythmic activity is still rather fragmentary. This stems in part from the fact that class-III activity of a compound was traditionally evaluated by assessing the prolongation of the action potential duration (e.g. at 50% and 90% of repolarisation, referred to as APD_{50} and APD_{90}, respectively), an approach that does not take into due account the possible contribution of different currents during repolarisation and therefore may classify drugs with pharmacologically distinct properties as belonging to the same group.

A few years ago, Morgan and Sullivan [11] published one of the most extensive reviews on structure–activity relationships for class-III anti-arrhythmic drugs and proposed the structural requirements for a class-III pharmacophore (Fig. 2): a *para*-substituted phenyl ring connected to a basic nitrogen via a highly variable linking chain. From a quick overview of the molecular structures of the compounds reported to prolong the QT interval and block HERG K^+ channels, it emerges that some molecules (e.g. terfenadine and astemizole) indeed satisfy the criteria to display class-III properties, whereas the class-III pharmacophore proposed by Morgan and Sullivan is not easily identifiable in other compounds (e.g. probucol and erythromycin). Of course, the possibility remains that a closer analysis might reveal that, in some cases, metabolites and not the parent compound are responsible for class-III

Table 2 Classes of drugs with QT-prolonging potential and possible mechanism(s) of action[a]

	Dose associated with QTc increase (ΔQTc recorded)[b]	Population	Reference	Possible mechanism(s) of action and additional information	Reference
Anti-psychotics					
Anti-psychotic medication	Long-term conventional doses (mean QTc 447 vs 417, treated vs untreated patients)	Patients with schizophrenia without cardiac disease	[2]	Prolonged QTc interval and QTc dispersion not associated with increased risk of ventricular tachyarrhythmia	[2]
	>4-week treatment with >2,000 mg chlorpromazine equivalents daily (odd ratio for prolonged QTc interval = 4.28)	In-patients	[36]	Several anti-psychotics exert class-III anti-arrhythmic effects at micromolar concentrations in vitro	[37, 38]
Thioridazine	50-mg single oral dose (22 ms)	Healthy volunteers	[39]		
	500 mg	Overdosage	[40]		
Chlorpromazine	100 mg daily	Case report	[41]		
Haloperidol	4 mg per os	Case report	[42]	Inhibition of HERG K^+ channels (both haloperidol and its reduced metabolite)	[48]
	50 mg per os daily	Case report	[43]		
	>50 mg i.v. (haloperidol or droperidol) (~25%)	Critically ill patients	[44, 45]		
	80 mg i.v. (total dosage 915 mg over 7 days) (184 ms)	Case report	[46]		
	>100 mg i.v. over 24 hours (~200 ms)	Critically ill patients	[47]		
Droperidol	0.1 mg·kg i.v. (37 ms)	Surgical patients	[49]		
Pimozide	6 mg orally (13.3 ms)	Healthy volunteers	[50]		
Sertindole	8–20 mg daily (~19 ms)	Patients in clinical trial	[51]	Inhibition of HERG K^+ channels ($IC_{50} = 14$ nmol·l^{-1})	[52]
Anti-depressants					
Desipramine	2.5 mg·kg^{-1} daily (40 ms)	Case report	[53]	Micromolar concentrations of imipramine (which is metabolised to desipramine) inhibit I_{Kr}	[54, 55]
Nortriptyline	0.51 mg·kg^{-1} daily (46 ms)	Case report	[56]		
Amitriptyline	No significant ΔQTc with 150–200 mg daily	Patients in clinical trial	[57]	Inhibition of heterologously expressed HERG potassium channels (micromolar concentrations)	[54]
Doxepin	Mean dose: 169 mg daily (22 ms)	Patients in clinical trial	[58]		
Fluoxetine	No significant ΔQTc up to a mean dose of 37 mg daily	Patients in clinical trial	[58]	Fluoxetine and its main metabolite norfluoxetine are CYP2D6 and 3A4 isoenzyme inhibitors	[51]
	No significant ΔQTc with 60–80 mg daily	Patients in clinical trial	[57]		
Anti-histamines					
Terfenadine	See Table 3			I_{Kr} inhibition via blockade of HERG K^+ channels	[59, 60, 61, 62]
				Kv1.5 inhibition (10-fold lower activity); at higher concentrations: I_{Na}, I_{Ca}, I_{Ks}, I_{K1}, I_{to} and $I_{K,ATP}$ inhibition	[59, 63, 64, 65, 66, 67, 68, 69]
				No significant difference in antihistamine activity and $K_v1.5$ inhibition between terfenadine enantiomers	[70, 71]
Astemizole	See Table 3			I_{Kr} inhibition (both astemizole and desmethylastemizole); I_{K1}, I_{to} inhibition	[24, 68, 72]
Mizolastine	No significant ΔQTc up to 40 mg daily	Healthy volunteers	[73]		

Fexofenadine	No significant ΔQTc up to 240 mg daily for 12 months	Healthy volunteers and patients with allergic rhinitis	[74]	Metabolite of terfenadine, considered free of arrhythmic potential	[59]
	180 mg daily (from 10 to 38 ms depending on the formula used to correct QT value)	Case report in susceptible patient	[75, 76]		
Loratadine	No significant ΔQTc up to 10 mg daily combined with 500 mg erythromycin	Healthy volunteers	[77]	Virtually inactive on HERG K^+ channels in non-human models and/or at room temperature	[78, 79]
				Inhibition of HERG K^+ channels in HEK 293 cells (IC_{50} = 173 nmol·l^{-1}) at a pacing rate of 0.1 Hz and 37 °C	[62]
				Kv1.5 inhibition; I_{to} inhibition in human atrium especially at 1–2 Hz pacing rate (relevance for rare cases of supraventricular arrhythmias?)	[80]
Cetirizine	No significant ΔQTc up to 60 mg daily	Healthy volunteers	[81]	No effect on HERG K^+ channel up to 30 μM	[79]
				I_{Kr} inhibition only at high concentration	[82]
Macrolides					
Erythromycin	500 mg i.v. infusion (20 ms)	Patients with pneumonia	[83]	CYP3A4 isoenzyme inhibitor	
	Mean dose: 42 mg·kg^{-1} daily i.v. (51 ms)	Retrospective study on all inpatients	[84]	I_{Kr} inhibition and, at higher doses, I_{Na} inhibition	[88]
	500–1,000 mg q.i.d. i.v. (220–278 ms)	Case reports	[85, 86]	Kv1.5 inhibition	[89]
	500–1,000 mg i.v. over 55–90 min (31 ms)	Critically ill patients	[87]		
Spiramycin	350,000 IU kg^{-1} daily (36 ms) orally	Newborns	[90]	No effect on CYP3A4 isoenzyme	[92]
	700,000 IU b.i.d. (135 ms) orally	Newborn	[91]		
Clarithromycin	500 mg b.i.d orally (3 ms)	Healthy volunteers	[93]	CYP3A4 isoenzyme inhibitor	
	500 mg b.i.d. orally (240 and 355 ms)	2 Critically ill patients (cor pulmonale, liver failure, renal failure)	[94]		
Anti-malarials				QTc changes may be associated with *falciparum* malaria independently of antimalarial therapy	[95]
Halofantrine	1000 mg daily (ΔQT ~ 80 ms)	Case report	[96]	The increase in QTc is dose-dependent and treatment with mefloquine during the previous month increases the slope of the halofantrine dose-response curve	[97]
Quinine	No significant ΔQTc up to 1800 mg daily (in a twice-daily oral dosing regimen)	Patients with arrhythmia	[98]	The stereoisomer quinidine is a class-IA anti-arrhythmic endowed also with class-III properties	[102, 103]
	600 mg i.v. t.i.d. (80 ms)	Patients with falciparum malaria	[99]		
	8.3 mg·kg^{-1} i.v. t.i.d. (41 ms)	Case in a clinical trial	[100]		
	10 mg·kg^{-1} i.v. infusion (ΔQTc ≤ 25%)	Healthy volunteers and patients with hepatitis	[101]		
Artemisinin and derivatives	Different regimens of artemisinin derivatives (prolonged QT values in 1.2% of 2638 patients)	Retrospective review of published and unpublished trials	[104]		
	No significant ΔQTc after a single oral dose of 100 mg artemether	Healthy volunteers	[105]		

Table 2 (Contd.)

	Dose associated with QTc increase (ΔQTc recorded)[b]	Population	Reference	Possible mechanism(s) of action and additional information	Reference
	i.m. Artemether (4 $mg \cdot kg^{-1}$ followed by 2 $mg \cdot kg^{-1}$ every 8 h for 72 h) vs i.m. quinine (20 $mg \cdot kg^{-1}$ followed by 10 $mg \cdot kg^{-1}$ every 8 h for 72 h): QT > 500 ms in 25% and 45% of patients, respectively	Patients with severe malaria	[106]		
Quinolones					
Gatifloxacin	200–800 mg (~ 3 ms)	[Data from the summary of the product characteristics]			
Grepafloxacin	600 mg daily (~ 2 ms)	Elderly subjects	[107]		
Levofloxacin	500 mg once daily (127 ms)	Case report (elderly woman with atrial fibrillation)	[108]		
Moxifloxacin	400 mg (6 ms)	[Data from the summary of the product characteristics]		Threshold concentration for class-III anti-arrhythmic effect: ~50 $\mu mol \cdot l^{-1}$	[109]
Sparfloxacin	200–400 mg single oral dose (4%)	Healthy volunteers	[110]	Increases in QTc are dose-related	[112]
	300–400 mg daily after loading dose (20–30 ms)	Healthy volunteers	[32]	Class-III anti-arrhythmic effects in vitro at concentrations ≥10 $\mu mol \cdot l^{-1}$	[113]
	200 mg daily for 10 days after loading dose (~10 ms)	Patients in phase-III trial	[111]		
Miscellanea					
Cisapride	10 mg q.i.d. (6 ms cisapride alone vs 25–26 ms if combined with clarithromycin)	Healthy volunteers	[93]	I_{Kr} inhibition via blockade of HERG K^+ channel (IC_{50} = 6.5–44.5 $nmol \cdot l^{-1}$)	[119, 120, 121, 122]
	Mean dose: 0.67 $mg \cdot kg^{-1}$ daily (10 ms)	Paediatric patients	[114]		
	Mean dose: 0.78 $mg \cdot kg^{-1}$ daily (31 ms)	Infants < 3 months of age	[115]		
	Mean dose: 0.81 $mg \cdot kg^{-1}$ daily (15.5 ms)	Paediatric patients	[116]		
	Mean dose: 0.84 $mg \cdot kg^{-1}$ daily (23 ms)	Newborns	[117]		
	Mean dose: 1.31 $mg \cdot kg^{-1}$ daily (74 ms)	Paediatric patients	[118]		
Glibenclamide	1.25–5 mg daily (11.4 ms)	Patients with type-2 diabetes mellitus compared with patients on diet only (but with lower prevalence of diabetic complications)	[123]	Autonomic neuropathy may per se prolong the QT interval	
				Inhibition of I_{to1}; blockade of HERG K^+ channels (IC_{50} = 74 $\mu mol \cdot l^{-1}$, i.e. above therapeutic concentrations)	[124, 125]
Ketanserin	40 mg daily (~130 ms)	Elderly patient	[126]	Class-III anti-arrhythmic effect (micromolar concentrations)	[129]
	40 mg b.i.d. (> 30 ms)	30% of patients in a clinical trial	[127]		
	40–80 mg daily (58 ms)	Six patients analysed retrospectively	[128]		
Ketoconazole	400 mg daily (5–10% increase in QTc in ~20% of 55 subjects)	Healthy volunteers	[130]	CYP3A4 inhibitor	
	200 mg b.i.d. orally (5.5 ms)	Healthy volunteers	[131]	I_{Kr} inhibition via blockade of HERG K^+ channels (IC_{50} = 49 $\mu mol \cdot l^{-1}$)	[132]
				In animal models, high doses of ketoconazole may mask the QT prolonging effect of H_1-receptor antagonists	[133]
Pentamidine	4 $mg \cdot kg^{-1}$ daily (120 ms)	HIV-infected patients	[134]		

Probucol	500 mg daily (13 ms)	Patients with hyperlipoproteinaemia	[135]		
	1000 mg daily (22 ms)	Patients with hypercholesterolaemia	[136]		
	Mean: 631 mg daily (45 ms)	Patients with hypercholesterolaemia	[137]		
	500 mg b.i.d. (160 ms)	Case report	[138]		
	500–1000 mg daily (QTc values ≥470 ms in 8% of women and 2% of men)	Retrospective review of published reports	[139]		
Tacrolimus (FK506)	2.5 mg i.v. b.i.d. (138 ms)	Case report (baseline QTc >450 ms)	[140]	I_{to} and I_K inhibition	[144]
	Dose not reported (52 ms)	Case report (concurrent treatment with digoxin)	[141, 142]		
	0.25 $mg \cdot h^{-1}$ i.v. (300 ms)	Case report	[143]		
Tamoxifen	100 $mg \cdot m^{-2}$ b.i.d. per os	2 Children in phase 1 study of high dose tamoxifen for refractory malignant gliomas	[145]	I_{Kr} and I_{Ca} inhibition (micromolar concentrations); concentrations causing sub-maximal inhibition of I_{Kr} have no significant effect on action potential duration	[147]
	≥80 $mg \cdot m^{-2}$ b.i.d. per os (10–20%)	Chemotherapy phase-I study in adult patients (combined with vinblastine)	[146]		
Terodiline	12.5 – 25 mg b.i.d. (20–300 ms)	Case series	[148]	I_{Kr} inhibition, I_{Ks} inhibition (20-fold lower activity than on I_{Kr}); I_{K1} inhibition	[151, 152, 153]
	12.5 mg b.i.d. (15 ms)	Elderly patients	[149]	$I_{Ca\text{-}L}$ inhibition and V_{max} reduction	[154]
	200 mg single dose (23 ms)	Healthy volunteers	[150]	R(+) enantiomer seems to be responsible for increased QTc	[150]

[a] The table includes some compounds that have been tested for their QT-prolonging potential, although they were found to have no effect on the QT interval at therapeutically effective doses

[b] ΔQTc (expressed in ms or as percentage variation) is provided where available: results from different studies may not be comparable because of different formulas used to correct the QT value

Table 3 Synopsis of pharmacodynamic and pharmacokinetic parameters in relation to the QT-prolonging potential of terfenadine and astemizole

	Terfenadine			Astemizole		
Dose associated with QTc increase (ΔQTc recorded)	60 mg b.i.d. (6–12 ms) 180 mg b.i.d. (19–26 ms)	Human subjects (healthy volunteers and patients with cardiovascular disease)	[155]	10 mg daily (86 ms)	Case report	[162]
				10 mg t.i.d. combined with erythromycin 250 mg q.i.d. (230 ms)	Case report	[163]
	60 mg b.i.d. combined with erythromycin 500 mg t.i.d. (64 ms)	Healthy volunteers (poor metabolisers)	[156]	10–20 mg daily combined with ketoconazole 50 mg daily (150 ms)	Case report	[164]
	60 mg b.i.d. combined with ketoconazole 200 mg b.i.d. (226 ms)	Case report	[157]			
	120 mg daily combined with ketoconazole 200 mg (100 ms)	Case report	[158]			
	60 mg b.i.d. combined with ketoconazole 200 mg b.i.d. (82 ms)	Healthy volunteers	[159]			
	120 mg daily combined with itraconazole 200 mg daily (41 ms)	Healthy volunteers	[160]			
	60 mg b.i.d. combined with grapefruit juice (19 ms)	Healthy volunteers (poor metabolisers)	[161]			
Concentration causing prolongation of action potential duration	10–30 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]	0.3–1.0 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]
				> 100 $nmol \cdot l^{-1}$	Rabbit purkinje fibres	[165]
Inhibition of I_{Kr} (IC_{50})	50 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]	1.5 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]
	96 $nmol \cdot l^{-1}$	Rabbit ventricular myocytes	[82]			
	180 $nmol \cdot l^{-1}$	Cat ventricular myocytes	[166]			
Inhibition of HERG K^+ channels (IC_{50})	56.0 $nmol \cdot l^{-1}$	Expressed in mouse L cells	[119]	48 $nmol \cdot l^{-1}$	Expressed in *Xenopus laevis* frog oocytes	[61]
	250–350 $nmol \cdot l^{-1}$	Expressed in *Xenopus laevis* frog oocytes	[61, 79, 167]	0.9 $nmol \cdot l^{-1}$	Expressed in HEK 293 cells	[24]
	204 $nmol \cdot l^{-1}$	Expressed in HEK 293 cells	[62]			
Inhibition of I_{Ks} (IC_{50})	~10,000 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[168]	No effect		[60]
Plasma concentration achieved at therapeutic doses (60–120 mg daily for terfenadine and 10 mg daily for astemizole)	Parent terfenadine usually undetectable (< 11 $nmol \cdot l^{-1}$)		[169]	Steady-state concentration: 0.28 $nmol \cdot l^{-1}$ (astemizole) ~11 $nmol \cdot l^{-1}$ (astemizole + desmethylastemizole)		[170]
	Peak concentration in poor metabolisers: 17 $nmol \cdot l^{-1}$		[161]			

Peak plasma concentrations reported during concomitant administration of CYP3A4 inhibitors (concentrations refer to the parent compound unless otherwise specified)	42 nmol·l^{-1}	With erythromycin in healthy volunteers (3 of 9 subjects)	[156]	1.8 nmol·l^{-1}	With itraconazole in healthy volunteers	[176]
	16 nmol·l^{-1}	With erythromycin in healthy volunteers (3 of 6 subjects)	[171]	0.9 nmol·l^{-1} (desmethylastemizole)	With itraconazole in healthy volunteers	[176]
	19 nmol·l^{-1}	With clarithromycin in healthy volunteers (4 of 6 subjects)	[171]			
	121 nmol·l^{-1}	With ketoconazole in case report	[157]			
	~53–170 nmol·l^{-1}	With ketoconazole in healthy volunteers (5 of 6 subjects)	[159]			
	59–204 nmol·l^{-1} (peak?)	With itraconazole in 2 case reports	[172, 173]			
	21–42 nmol·l^{-1}	With itraconazole in healthy volunteers	[160]			
	15–25 nmol·l^{-1}	With grapefruit juice in healthy volunteers	[161, 174, 175]			
% Plasma protein binding	97		[177]	97		[178]
Volume of distribution	Not reported		[178]	~45 l·kg^{-1}		[170]
Main metabolites	Fexofenadine (MDL 16455; terfenadine carboxylate): H_1-receptor antagonist with no effect on QT interval			Desmethylastemizole (same activity as parent compound as H_1-receptor antagonist and HERG K^+ channel blocker with an apparent elimination half-life of 9.5 days), norastemizole, 6-hydroxy-desmethylastemizole		[24, 170]
Relative risk (adjusted for age and gender) for ventricular arrhythmias (non use = 1; case control analysis)	2.0		[27]	17.8		[27]

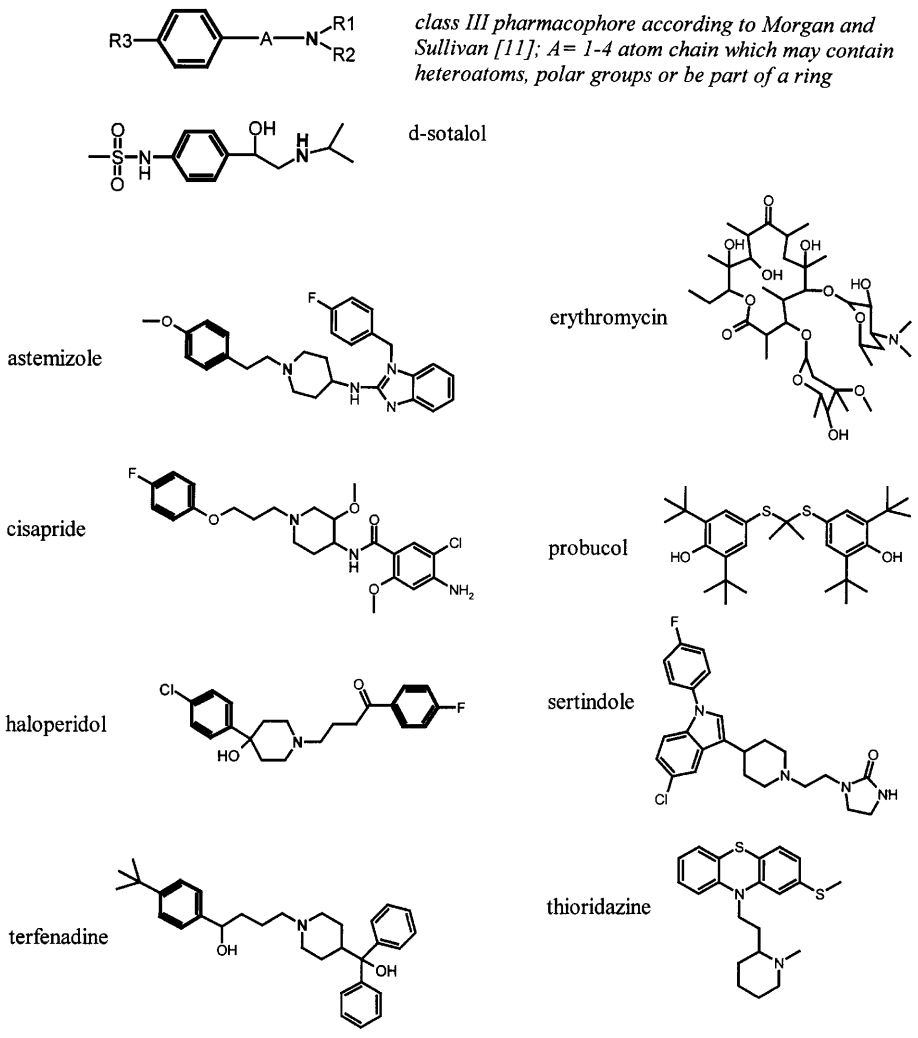

Fig. 2 Molecular structures of some drugs associated with QT-prolongation or torsades de pointes in relation to the pharmacophore proposed to carry class-III antiarrhythmic properties by Morgan and Sullivan [11]. On the *left*, examples of drugs in which this pharmacophore (a phenyl ring connected to a basic nitrogen via a linking chain) can be recognised. On the *right*, examples of drugs with reported QT-prolonging potential in which this pharmacophore is not easily identifiable

effects or that currents other than HERG-related K^+ currents are responsible for QT-interval prolongation and/or occurrence of life-threatening arrhythmias. In addition, lipophilicity and/or bulkiness of substitutions on the molecular structure may be crucial parameters conferring varying degrees of K^+-channel-blocking activity. For instance, terfenadine carboxylate (fexofenadine), the main metabolite of terfenadine, is a more polar compound having virtually no effects on QTc, apart from an isolated report in a susceptible patient (Table 2).

In any case, an important acquisition of the past decade is that cardiac adverse effects are not necessarily an intrinsic class effect: in the case of H_1-receptor antagonists [1], there is no correlation between the antihistaminic potency and the action potential prolonging effect. Likewise, as regards gastrointestinal prokinetic agents (in particular, 5-HT_4 receptor agonists), several lines of evidence suggest that blockade of HERG K^+ channels rather than stimulation of atrial 5-HT_4 receptors is responsible for QT prolongation [12, 13].

Interpretation of data from preclinical/in vitro studies

The role of preclinical screening methods is highly debated, because of the inherent differences between animal models and humans. However, a recent review [14] shows that, if properly conducted, in vitro and in vivo assessment of class-III properties of an investigational drug provides useful information and suggests that either method alone may be sufficient for the preclinical evaluation of the QT-prolonging potential. Several laboratories are indeed refining methods to study this aspect in animal models [15, 16, 17, 18, 19, 20, 21]. Although in vitro electrophysiological studies offer valuable information on arrhythmogenic mechanism(s), it should be kept in mind that proving that a drug has no effect on HERG-related currents does not automatically rule out the possibility of a clinically significant prolongation of the QT interval or the risk of potentially harmful arrhythmias. By contrast, detection of an effect on potassium channels does not invariably raise serious QT-related concerns on the clinical use of the

compound. For instance, the 5-HT_3-receptor antagonist ondansetron prolongs action potential duration by blocking I_K with a K_D of 1.7 μM in feline ventricular myocytes [22] and prolongs the QTc interval in dogs at doses of 2.63 $mg \cdot kg^{-1}$ i.v. or more [23]. However, present clinical experience and the fact that concentrations blocking I_K are well above concentrations at which 5-HT_3 receptors are inhibited do not suggest a significant cardiotoxic potential.

A major problem in interpreting results obtained in preclinical/in vitro electrophysiological studies (IC_{50} for inhibition of K^+ currents, IC_{50} for prolongation of action potential duration, etc.) is that a careful scrutiny of the pharmacokinetic properties of the compound is mandatory to allow meaningful comparisons between in vitro and plasma concentrations. Plasma concentrations in humans should be considered along with the apparent volume of distribution, the metabolic pathways (metabolites may retain QT prolonging potential, be even more active, or be devoid of such an effect), and the mode of elimination. The threshold concentration (or the IC_{50}) for a class-III effect in vitro may be higher than peak plasma concentrations achieved at therapeutic doses, but tissue concentrations (specifically, cardiac tissue concentrations) may exceed those found in plasma if the drug has a large volume of distribution. One example is provided by the comparison of pharmacodynamic/pharmacokinetic parameters of terfenadine and astemizole reported in Table 3. Terfenadine is readily metabolised to fexofenadine, which maintains good H_1-receptor blocking activity, but has no effect on the QT interval even at doses well above the therapeutic ones. Unmetabolised terfenadine plasma concentrations are usually below detection limits ($5\ ng \cdot ml^{-1}$ or $11\ nmol \cdot l^{-1}$, in most studies), but may become detectable in case of pharmacokinetic interactions with drugs known to inhibit the CYP3A4 isoenzyme, in case of overdosage or concomitant hepatic disease. On the contrary, two of the main metabolites of astemizole (desmethylastemizole and norastemizole) retain the ability to block HERG K^+ currents at nanomolar concentrations [24]. In addition, the large volume of distribution of astemizole (indicating extensive tissue penetration: indeed, the concentration in cardiac muscle is estimated to be more than 100 times as high as the plasma concentration [25, 26]) and the long elimination half-life of desmethylastemizole (about 9.5 days) suggest a higher risk of potentially harmful effects on cardiac repolarisation with astemizole than with terfenadine. This prediction based on pharmacokinetic/pharmacodynamic data is in good agreement with a recent case-control study, which calculated that the relative risk of ventricular arrhythmias (adjusted for age and gender) was 2.0 for terfenadine and 17.8 for astemizole (non-use = 1) [27].

Clinical relevance

Although asymptomatic prolongation of the QT interval is a useful marker of the cardiotoxic potential of a drug, it is only a surrogate marker of cardiotoxicity and it is difficult to establish the threshold for a clinically significant prolongation of the QT interval. Thus, identification of risk factors that may precipitate prolongation of the QT interval into life-threatening arrhythmias becomes an important issue (see Table 4 for a synopsis). Widespread knowledge of these risk factors should help to avoid misprescriptions leading to cardiotoxicity.

The clinical use of drugs that are known to prolong the QT interval is not necessarily associated with an increased occurrence of ventricular arrhythmias, unless high dosage, i.v. route of administration (especially at high injection rates: e.g. erythromycin) or concomitant metabolic inhibitors are used or other risk factors (Table 4) coexist. For instance, a recent study suggests that long-term anti-psychotic medication at conventional doses does not increase ventricular tachyarrhythmias in patients without cardiac disease, despite evidence for prolonged QTc interval and QTc dispersion [2]. Further clinical studies with appropriate statistical power should evaluate the cardiotoxic potential of currently licensed drugs that fall into one of those classes

Table 4 Risk factors for the occurrence of torsades de pointes[a]

Subject related
Congenital long QT syndrome; QTc > 440 ms; increased QT dispersion
Female gender
Clinically significant bradycardia (< 50 beats per minute), history of symptomatic arrhythmias or any other clinically significant heart disease
Electrolyte imbalance (especially hypokalaemia, hypomagnesaemia)
Impaired hepatic/renal function
Hypothyroidism
Drug-related
Concomitant treatment with drugs with known potential for
Pharmacokinetic interactions with CYP3A4 isoenzyme inhibitors: e.g., serotonin reuptake inhibitors, HIV protease inhibitors, zileuton
Pharmacokinetic (inhibition of CYP3A isoenzyme)/pharmacodynamic (intrinsic class III effect) interactions: e.g. macrolide antibacterials (e.g. erythromycin), azole antifungals (e.g. ketoconazole)
Pharmacodynamic interactions: e.g. anti-arrhythmics (class I and III), drugs inducing electrolyte imbalance such as diuretics (risk of hypokalaemia)

[a] A recent paper provides useful information to discriminate electrocardiographic artefacts mimicking ventricular tachycardia [179]

with recognised QT-prolonging effect and guide the risk–benefit assessment of these compounds.

Concerning newly licensed drugs, the availability of many new agents and changes in medication consumption patterns over the years threaten to exacerbate problems such as misprescribing, medication errors and undetected interactions. In this setting, post-marketing surveillance becomes essential in ensuring drug safety [28]. Although the right solution to misprescribing of a useful drug with a significant, albeit minor, cardiotoxic potential is not necessarily its withdrawal from the market, it should be acknowledged that, in some cases, the complexities of prescribing information may be difficult to implement. The potential for drug interactions (namely those inhibiting the CYP3A4 isoenzyme [29]) is receiving increasing attention both from drug companies and regulatory agencies. The withdrawal of mibefradil in 1998 may be taken as an example of a drug with a sound pharmacological rationale that was difficult to use in a clinical setting because of the potential for drug interactions via CYP3A4 isoenzyme inhibition.

Standardization of procedures for regulatory purposes

There are several recent examples of the great impact that the finding of a QT-prolonging effect by non-cardiac drugs during clinical trials has on drug development [30, 31]. A recent paper [32] outlines the various actions that were taken in phase I–III studies to evaluate the electrocardiographic and cardiovascular safety data of sparfloxacin in accordance with the suggestions of an independent international safety board.

The ongoing discussion on the QT-prolonging potential of non-cardiac drugs and its clinical significance does not allow us to provide strict guidelines to standardise procedures to be followed in the event that a new investigational drug turns out to affect the QT interval. However, the European Agency (EMEA) issued a document [33] that offers a useful starting point and should be revised periodically to keep pace with ongoing developments. In this document, the problems encountered in obtaining reliable and meaningful measurements of drug-induced changes of the QT interval in preclinical and clinical studies are briefly discussed. These problems are also outlined in Table 5.

Several authors have already drawn the attention to the inherent difficulties involved in accurate measurement of the QT interval. A recent review [34] discusses possible answers to issues related to QTc prolongation by non-cardiac drugs (e.g. what is the desired outcome? what is the dependent variable to be measured? what is the appropriate statistical analysis?). For the evaluation of potential clinical risks associated with QTc changes, individual QTc changes rather than mean values for study populations should be used. Moreover, while changes in QTc indicate a drug effect, absolute QTc values have greater prognostic significance for the occurrence of tachyarrhythmias. In the EMEA document [33], the following general guidelines are given on QTc changes (using the Bazett's correction) relative to baseline measurements (see also [34] for a discussion): (1) individual changes below 30 ms are generally thought unlikely to raise significant concerns about the potential risk of arrhythmias; (2) individual changes between 30 ms and 60 ms are more likely to represent a drug effect and raise concern about the potential risk of arrhythmias; and (3) individual changes greater than 60 ms raise clear concerns about the potential risk of arrhythmias.

The possible use of QT dispersion rather than QT prolongation as a risk predictor is also being investi-

Table 5 Problems encountered in obtaining reliable and meaningful measurements of drug-induced changes of the QT interval

Patient variability
High intraindividual (circadian variation; law of regression to the mean [180]) and interindividual variability (males vs females; infants vs adults) in QTc values
Variability in the individual metabolic capacity for a given drug
Measurement of QT interval
Variability in the heart rate (different formulas to correct the QT value for heart rate)
Changes in T wave morphology and occurrence of U waves (may be important warning signs and precede the occurrence of torsades de pointes)
Lack of a strict definition of normal and abnormal values
Lack of reliable correlation between readings from Holter recordings and standard ECG
Lack of standardisation of automated ECG readings
Pharmacokinetics
Timing of ECG measurements with respect to peak/steady state drug plasma concentrations
Need to consider plasma concentrations of both parent drug and its significant metabolites (especially if they display class-III anti-arrhythmic effects)
Need for enantioselective methods to monitor plasma concentrations of racemic compounds
Data analysis and interpretation
Definition of the dependent variable (raw QTc interval vs maximal QTc interval vs maximal QTc change from baseline vs area under the QTc interval-time curve vs QTc dispersion; see ref. [34])
Statistical power of the study
What is the threshold for a clinically significant change in QTc/QT dispersion?

gated [2, 33]. Increased QT dispersion (i.e. the difference between the maximum and minimum QT across the 12-lead ECG) is considered a marker of uneven cardiac repolarisation. Although the cellular basis for QT dispersion is not completely understood, interest in this parameter has been fuelled by the finding in animal studies that increased dispersion lowers the ventricular fibrillation threshold and facilitates induction of re-entrant arrhythmias. Clinically, QT dispersion is being investigated as a predictor of long-term mortality in patients with acute myocardial infarction and clinical evidence of heart failure [35].

Several cases should be considered when characterising the effects of non-cardiac drugs on QTc intervals: a compound may have no effect on QTc; it may have a minor effect that is considered clinically insignificant; and, in rare instances, there may be a clinically significant effect, but the risk at therapeutic doses may be overwhelmed by the benefit achieved in a specific clinical condition for which no alternatives are available.

A crucial issue in the evaluation of studies reporting no effect of a given compound on the QT interval is the statistical power of the study. Insufficient statistical evidence for a difference does not necessarily mean that there is no difference, and studies reporting the effects on QT interval should always discuss their statistical power. This issue should be kept in mind when considering some of the early studies reported in Table 2, which were not specifically designed to detect changes in QT interval.

When a non-cardiac drug significantly affects the QTc interval, the overall clinical significance depends on a number of parameters (dose–response relationship; likelihood of pharmacokinetic interactions, etc.) that should be evaluated in relation to the proposed clinical use. Consistency in this evaluation process for regulatory purposes is mandatory.

Looking for European Public Assessment Reports at the EMEA internet site, we found that documents concerning the following non-cardiac drugs mentioned effects on the QT interval: alatrofloxacin, emedastine, levoacetylmethadol, mizolastine, olanzapine, samarium [^{153}Sm] lexidronam pentasodium, sparfloxacin and trovafloxacin.

Levoacetylmethadol is an example of a drug which, although prolonging the QT interval, was recently licensed by the European Agency (EMEA), with the recommendation to perform additional comparative studies with methadone as well as in vitro electrophysiological studies to evaluate the risk of cardiac conduction and repolarisation changes.

In our opinion, licensing a new non-cardiac drug with QT-prolonging potential, with the recommendation to perform additional studies, may be justified when major innovation is achieved with respect to existing therapies. On the contrary, if the compound does not represent significant innovation, the recommendation to perform additional studies on the QT-prolonging effect should be a prerequisite to obtain marketing authorisation.

Future perspectives

In the next few years, basic and clinical pharmacologists will have to address a number of issues concerning the re-assessment of licensed medicinal products and new drug development.

For currently licensed non-cardiac drugs with QT-prolonging potential, a formal assessment (pharmacoepidemiological studies) of relative risks for patients exposed to these agents will enable a formal risk–benefit assessment and identification of possible additional risk factors due to the underlying disease or concomitant medication. In case risk factors are identified, amendment of the summary of product characteristics is a necessary step, but often turns out to be ineffective to ensure safe drug utilisation. Amendments to the summary of product characteristics combined with ''Dear Doctor letters'' seems to be a more appropriate action.

For investigational new drugs, the following needs emerge:

1. Structure–activity studies joining the efforts of medicinal chemists and molecular pharmacologists could lead to associate a definite pharmacophore with an action on a specific ion channel, hence on a given portion of the atrial and/or ventricular action potential; this *in silico* approach will help the preclinical development of investigational new drugs.
2. Standardisation of procedures in preclinical in vitro and in vivo studies (especially as regards QT measurements) to screen those molecules having a QT-prolonging potential on the basis of *in silico* predictions.
3. Carefully designed phase I–III studies, especially for those drugs that appear to have a discrete, albeit small, effect on the QT in preclinical tests. In these cases, it would be unwise to try ''to prove the null hypothesis'' (which, strictly speaking, can never be proven) resorting to studies that claim no difference between drug and placebo with inadequate statistical power. Identifying the percentage of ''outliers'' (i.e. those patients that have greater QT prolongation) may also be a useful guide to assess risk in subjects treated with a new agent versus comparators. Parallel in vitro electrophysiological studies will help to define the pharmacological profile and cardiotoxic potential of these investigational new drugs and may become part of standard regulatory requirements.

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