Drug-Induced Arrhythmia

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Prolongation of the QTc interval has been associated with proarrhythmia resulting from a potentially fatal form of polymorphic ventricular tachycardia called torsades de pointes (TdP). Genetic forms of the long-QT syndrome (LQTS) associated with high arrhythmic risk have been causally related to mutations in ion channels responsible for the cardiac action potential; genetic factors associated with milder degrees of QTc prolongation and arrhythmic risk have also been described. Acquired forms of QTc prolongation and proarrhythmia, particularly related to drug therapy, are frequently related to drug effects on the same ion channels involved in genetic forms of LQTS. As is true for genetic forms of LQTS, there is a wide spectrum of potential drug effects on the QTc interval ranging from trivial to potentially lethal. Drug-induced QTc prolongation is a complicated phenomenon related not just to the properties or dose of a particular drug but also to drug-drug interactions and a variety of patient factors, including age, gender, the presence and severity of underlying heart disease, and genetic predisposition. Additionally, drug effects on other ion channels, including blockade of sodium channels (causing prolongation of the QRS interval rather than the QTc interval), are an important cause of drug-induced proarrhythmia.

The purpose of this review is to summarize the available data related to acquired forms of LQTS, with particular focus on drug-related QTc and proarrhythmia. A brief summary is presented here of genetic LQTS because the relevant genes and proteins form the basis for an understanding of the causes of acquired LQTS, and in any given patient, the QTc is determined by genetic, substrate, and environmental factors. Emphasis is placed on practical strategies for clinicians, with the goal of minimizing the risk of dangerous proarrhythmia related to the use of both cardiac and noncardiac drugs with the potential for QTc prolongation.

Genetic Basis of LQTS

Genetic forms of the LQTS can be associated with a markedly increased risk of TdP and sudden cardiac death (SCD), and the mechanisms elucidated through analysis of genetic LQTS have provided considerable insight into acquired forms of LQTS. Genetic defects associated with profound increases in QTc have frequently been associated with either a reduction in an outward potassium current (via $I_{K_s}$: LQT1 and LQT5; or via $I_{Kr}$: LQT2 and LQT6) or augmentation of an inward sodium current ($I_{Na}$: LQT3) or calcium current. These classic forms of LQTS are associated with different T-wave morphologies and arrhythmic triggers based on the particular form of LQTS, although substantial overlap exists. Other variants of genetic LQTS have been associated with proteins that affect trafficking or function of ion channels such as ankyrin 2 (LQT4) or a variety of proteins that affect ion channel kinetics (reviewed elsewhere). Additionally, the genetic short-QT syndrome has been described as being related to gain-of-function mutations in potassium channels or loss-of-function mutations in calcium channels. Like LQTS, the short-QT syndrome can also be associated with substantial arrhythmic risk.

Classic forms of familial LQTS associated with (often) marked prolongation of the QTc interval and arrhythmic risk are relatively rare disorders, even in aggregate. Interestingly, however, recent studies suggest that a substantial proportion of victims of previously unexplained SCD may harbor mutations in proteins encoding ion channels associated with the genetic LQTS. Furthermore, missense mutations in genes associated with the LQTS (encoding cardiac sodium and potassium channels) are relatively common in the general population, although the functional impact of most of these mutations is currently unknown. Relatively common genetic variants in genes encoding cardiac ion channels have been associated with QTc prolongation, and QTc effects have been noted to be associated with mutations in genes not associated with classic forms of LQTS such as NOS1AP.

Genetic forms of the LQTS therefore represent a wide spectrum of diseases. The classic but relatively rare genetic LQTS may be associated with substantial QTc prolongation and arrhythmic risk, even in the absence of additional risk amplifiers such as the use of QTc-lengthening drugs (although the risk of arrhythmia in the classic forms of genetic LQTS can be markedly increased by the addition of these risk amplifiers). LQTS may exhibit incomplete penetrance based on standard ECG criteria, with a reported penetrance of 25% for gene carriers of classic LQTS mutations and a sensitivity of 38% for conventional clinical diagnostic criteria in detecting these mutations in 1 study of familial LQTS. Patients with classic LQTS mutations but normal or borderline QTc intervals are generally much more susceptible to QTc-prolonging medications compared with the general population, yet they may be difficult to detect before drug exposure.
There are also many common genetic variants, some of which are described above, that may be associated with milder degrees of QTc prolongation and arrhythmic risk. These variants are currently not recognized in the vast majority of patients who harbor the mutations, and the QTc in baseline ECGs from these patients may fall within the normal or borderline range. These patients may have substantially reduced repolarization reserve, however, and they may be at greater risk than the general population for QTc prolongation and TdP when exposed to risk amplifiers such as QTc-prolonging drugs.17

**Drug-Induced QTc Prolongation**

Syncope related to the use of quinidine was first described in the 1920s. Initially, the cause of this syncope was not understood, but in the 1960s, a drug-related, pause-dependent form of polymorphic ventricular tachycardia was identified by Selzer and Wray.18 Quinidine-associated syncope and paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias, later called TdP by DESERTEMNE,19 was then described on the basis of the characteristic undulating pattern of the polymorphic ventricular tachycardia on the surface ECG. Arrhythmias related to noncardiac medications, including antihistamines and antipsychotics, were also reported in the 1960s and 1970s, but they were also poorly understood by clinicians. In the ensuing decades, the mechanism of these arrhythmias, namely QTc prolongation leading to TdP, was elucidated, and this is now a major focus of drug development and regulatory oversight.

Most clinically relevant drug-related QTc prolongation occurs via inhibition of IKr, a potassium current mediated in humans by the ion channel KCNH2 encoded by the human ether-a-go-go–related gene (HERG), analogous to the genetic LQT2 form of the disease. Molecular work on the HERG channel has allowed the creation of models of drug interaction with HERG20 (Figure 1). HERG is considered a “promiscuous” channel in that it binds to and is frequently inhibited by a wide variety of structurally diverse chemicals. X-ray crystallography and site-directed mutagenesis have been used to identify the interaction of drugs with the inner cavity of HERG and have provided a molecular explanation for the relatively frequent impact of drugs on the channel.21 Other mechanisms for drug-induced QTc prolongation include blockade of both IKr and IKs by azimilide22 and inhibition of HERG trafficking to the cell membrane by pentamidine and arsenic trioxide.23,24 Interestingly, fluoxetine, a widely prescribed antidepressant, has been found to prolong the QTc interval by 2 mechanisms: direct block of the HERG channel and disruption of HERG trafficking to the cardiac cell membrane.25 Because most older drugs used in clinical practice have not been well studied with regard to their effects on ion channel physiology, some of these effects may be more common than currently appreciated.

The drugs that carry the greatest risk for marked QTc prolongation and TdP are class III (and some older class I) antiarrhythmic drugs (including sotalol, dofetilide, ibutilide, and azimilide), for which HERG inhibition and QTc prolongation are part of the therapeutic mechanism of action. Among these agents, observed rates of TdP of ≥1% have been described when the drugs are used in clinically relevant doses.26,27 These drugs are typically used by specialists in cardiovascular disease and cardiac electrophysiology who are aware of the potential proarrhythmic risk. Avoidance of the use of these agents in patients at highest risk for drug-induced TdP and careful monitoring for QTc-prolonging effects, often with inpatient initiation of drug therapy, are recommended and at times mandated by regulatory agencies and help minimize the risk of potentially life-threatening drug-induced arrhythmias.

Figure 1. Docking of clofilium within the inner cavity of a homology model of the HERG channel. Twenty different binding modes were generated with either the chlorophenyl group or the aliphatic tail of clofilium oriented toward the selectivity filter end of the cavity. Side view of 1 possible binding mode that is highly consistent with the experimental results. The SS to S6 domains of the channel are represented by shaded ribbons, with the 4 subunits distinguished by different colors. Clofilium is shown with the chlorine (green) oriented toward the selectivity filter. Clofilium carbon atoms are shown in gray; hydrogen atoms are shown in cyan. Reproduced with permission of the publisher from Perry et al.20 Copyright © 2004, the American Society for Pharmacology and Experimental Therapeutics.
important predictor of arrhythmia susceptibility, likely related to its effects on intracellular calcium overload and early afterdepolarizations.\textsuperscript{39} Spatial heterogeneity or dispersion of repolarization across the ventricular wall (transmural dispersion of repolarization) is among the strongest preclinical predictors of the potential of a drug to cause TdP.\textsuperscript{38} This heterogeneity of repolarization relates to the differing properties of the epicardial, midmyocardial (M cells), and endocardial cells and to the heightened susceptibility of M cells to the action potential–prolonging effects of drugs that selectively block I_{Kr} (Figure 3).\textsuperscript{40} Despite its significant limitations as a surrogate marker, the QTc interval remains the best established clinical predictor of drug-mediated proarrhythmic risk.\textsuperscript{41}

**Drug-Drug Interactions**

Clinical cases of TdP are frequently related to polypharmacy and drug-drug interactions (Figure 4). These interactions may take a variety of forms in clinical practice. Among the most common of these are pharmacodynamic interactions in which multiple agents with HERG-blocking properties are inadvertently prescribed for a patient. A typical example of this type of interaction is a patient who has been taking a stable dose of a class III antiarrhythmic agent for atrial fibrillation and is then prescribed a quinolone antibiotic for an acute infection. In such a case, the physician who prescribed the antiarrhythmic drug (likely a cardiovascular specialist or electrophysiologist who is aware of the arrhythmic risk) may be unaware and uninvolved in the decision to prescribe the antibiotic, which might occur in a primary care or urgent care facility. This type of polypharmacy is quite common in clinical practice. A review of medication records of >1 million patients identified the use of at least 1 QTc-prolonging medication in \( \approx 23\% \) of patients, the use of 2 agents in >9% of patients, and the use of \( \approx 3 \) agents in 0.7% of patients.\textsuperscript{42} Although these interactions rarely result in adverse outcomes, a substantial proportion of the cases of drug-induced TdP encountered in clinical practice are confounded by the concomitant use of multiple contraindicated drugs.

Another common mechanism by which polypharmacy leads to QTc prolongation and arrhythmic risk relates to drug metabolism and pharmacokinetic drug-drug interactions.\textsuperscript{43} The sentinel historic example of this form of drug interaction is the concomitant use of terfenadine and inhibitors of the

![Figure 2. The relationship between ventricular transmembrane action potentials (APs) and the surface ECG.](image-url)

**Figure 2.** The relationship between ventricular transmembrane action potentials (APs) and the surface ECG. In the ECG traces, the QRS and QT intervals reflect depolarization and repolarization, respectively, of the ventricles. An increase in the AP duration is responsible for the prolongation of the QT interval. Shown on the left are the APs and ECG in the absence (control) and presence of a drug (eg, a blocker of I_{Kr}) that prolongs the AP duration and consequently the QT interval. Shown on the right are 2 early afterdepolarizations (EADs) occurring during the repolarization phase of a prolonged AP, giving rise to 2 ectopic beats (EBs) in the ECG. Reproduced with permission of the publisher from Belardinelli et al.\textsuperscript{37} Copyright © 2003, Elsevier.

![Figure 3. Effects of a specific I_{Kr} blocker, erythromycin, on transmembrane activity recorded from epicardial (Epi), endocardial (Endo), and deep subepicardial (M cell) sites in a transmural strip of canine left ventricle.](image-url)

**Figure 3.** Effects of a specific I_{Kr} blocker, erythromycin, on transmembrane activity recorded from epicardial (Epi), endocardial (Endo), and deep subepicardial (M cell) sites in a transmural strip of canine left ventricle. Each panel shows superimposed action potentials recorded at basic cycle lengths (BCLs) of 1000 to 8000 milliseconds. A, Control. B, Recorded after 30 minutes of exposure to 10 \( \mu \)g/mL erythromycin. C, Recorded 30 minutes after the concentration of erythromycin was increased to 100 \( \mu \)g/mL. Reproduced with permission of the publisher from Antzelevitch et al.\textsuperscript{40} Copyright © 1999, Wiley-Blackwell.
enzyme by which it is metabolized, cytochrome P450 3A4. Terfenadine was a widely prescribed nonsedating antihista-
mime before its withdrawal from the market in 1998. Terfe-
nadine has potent HERG channel–blocking activity and can
prolong the QTc interval, although at standard clinical doses,
the drug is associated with relatively minor QTc prolongation
and low proarrhythmic risk when used as monotherapy (QTc
prolongation, \( \approx 18 \) milliseconds at peak plasma concen-
trations). However, despite the apparent safety of the drug in
large postapproval studies, rare cases of fatal TdP associated
with terfenadine were reported. Further studies subsequently
revealed that the route of terfenadine metabolism explained
its elevated arrhythmic risk. Terfenadine undergoes ex-
tensive hepatic first-pass metabolism by the cytochrome P450
3A4 (CYP3A4) system to its active metabolite (which has
antihistaminic but not HERG-blocking properties). CYP3A4
activity can be inhibited by a wide variety of approved drugs
that are commonly used in clinical practice, including certain
antibiotics, antifungals, cimetidine, fluoxetine, and amiod-
arone. In the presence of a potent CYP3A4 inhibitor such
as ketoconazole, systemic levels of terfenadine may be
increased up to 20-fold, leading to marked QTc prolongation

Figure 4. An example of QTc prolongation and TdP associated with the combined administration of methadone and voriconazole. A
47-year-old woman with a history of intravenous drug abuse was on long-term treatment with methadone, a drug known to prolong the
QTc interval. On methadone, her QTc interval was 420 ms (A). She then developed a fungal lung infection, and voriconazole treatment
(which can both prolong the QTc interval and slow metabolism of methadone) was initiated. She subsequently suffered an out-of-
hospital cardiac arrest requiring defibrillation. An ECG (while she was on methadone and voriconazole) demonstrated a QTc interval of
594 ms (B). In the hospital, she had multiple runs of TdP. Note that a premature ventricular contraction causes a compensatory pause
followed by a sinus beat and a second premature ventricular contraction that initiates polymorphic ventricular tachycardia, a classic
pause-dependent initiation sequence for TdP (C). She was ultimately treated with an implantable cardioverter-defibrillator.
and an elevated risk of TdP. Given the availability of other antihistamines that lack proarrhythmic risk and the difficulty of managing the large number of potentially dangerous drug-drug interactions with terfenadine, this drug was withdrawn from the market once this important pharmacokinetic interaction and its associated risk were elucidated. Interestingly, fexofenadine (Allegra), the active metabolite of terfenadine that does not affect the QTC interval, is now a widely prescribed antihistamine.

Other drug-drug interactions can also predispose to arrhythmia. The use of a drug such as a diuretic may cause hypokalemia and hypomagnesemia, which can further prolong the QTc interval and predispose to arrhythmia in the setting of an HERG-blocking agent. A case of acquired LQTS and Brugada syndrome has been described in the setting of indapamide-induced hypotremia and hypokalemia. Other drugs such as aminoglycoside antibiotics can impair renal function, leading to higher and potentially toxic levels of HERG-blocking agents such as sotalol and dofetilide that are cleared renally.

**Risk Amplifiers for QTc Prolongation**

Experimental models for HERG blockade and TdP may be created in tightly controlled laboratory conditions, but clinical QTc prolongation and arrhythmia occur in patients and are highly dependent on individual patient-specific factors. These factors can be considered risk amplifiers, which, when considered together, can help predict the arrhythmic risk in a given patient. Two of these factors include genetic predisposition (clinical and subclinical forms of genetic LQTS) and various drug-drug interactions as described above.

Multiple other risk amplifiers also may contribute to arrhythmic risk; among the most common is female gender. Women have longer average QTc intervals at baseline compared with men and are at increased risk of drug-induced QTc prolongation and arrhythmia. It has been reported that ≈70% of drug-associated TdP occurs in women. Another common factor is age; reduced repolarization reserve and the risk for drug-induced QTc prolongation and TdP are higher in the elderly (who are also frequently exposed to polypharmacy). Other risk amplifiers include hypokalemia, hypomagnesemia, bradycardia, and the presence of underlying structural heart disease, particularly ventricular hypertrophy and congestive heart failure.

Most episodes of clinical, drug-induced TdP occur in the setting of multiple risk amplifiers. An assessment of TdP associated with noncardiac drugs found evidence of risk factors (including heart disease, female gender, LQTS, electrolyte abnormalities, drug interactions, or high drug doses) in the vast majority of cases examined, and the majority of cases had 2 or more of these risk factors. Avoidance of clinical TdP is therefore an issue not only of correctly recognizing a drug with the capacity to prolong the QTc interval but also of assessing that risk in each individual patient. A drug that may be given safely at a certain dose to one patient may be exceedingly dangerous when given at the same dose to a patient at high risk for drug-induced QTc prolongation and TdP.

**Drug-Induced Arrhythmia Related to Sodium Channel Blockers**

Although delayed cardiac repolarization (manifest as QTc prolongation) is the most common cause of drug-related proarrhythmia, agents that slow the rate of cardiac depolarization (manifest as QRS prolongation on surface ECG) can also cause life-threatening ventricular arrhythmias and SCD. Sodium channel blockers cause marked rate-dependent slowing of conduction in ischemic and infarcted myocardium and may thereby promote heterogeneity of conduction and facilitate the initiation of reentrant wave fronts around lines of functional conduction block, resulting in ventricular tachycardia. Clinical observations suggesting that antiarrhythmic drugs might contribute to SCD by mechanisms other than QTc prolongation were made >25 years ago. This report related to the use of class IA antiarrhythmic drugs such as quinidine and disopyramide, which affect both cardiac depolarization and repolarization. In this small case series, it was postulated that slowing of conduction in diseased myocardium might be responsible for the proarrhythmic effects observed, because QTc interval prolongation was not present and most patients had provokable arrhythmias in response to programmed ventricular stimulation in the presence, but not in the absence, of the offending antiarrhythmic drug. Subsequently, the Cardiac Arrhythmia Suppression Trial (CAST), a double-blind, randomized, placebo-controlled trial in patients with prior myocardial infarction and ventricular ectopic activity, demonstrated excess all-cause and arrhythmic mortality in patients randomized to the class IC antiarrhythmic drugs flecainide and encainide, both potent sodium channel blockers with little effect on repolarization. The use of flecainide or encainide was associated with a 3.6-fold increase in the risk of fatal arrhythmias and nonfatal cardiac arrests compared with placebo. In addition to this direct arrhythmogenic effect, these potent sodium channel–blocking drugs seemed to convert both ischemic and heart failure events to fatal outcomes. The results of CAST established definitively the fact that pharmacological inhibition of cardiac depolarization by sodium channel blockade can, like pharmacologically induced prolongation of repolarization, lead to ventricular proarrrhythmia and SCD. Although the precise pathophysiological basis of these proarrhythmic effects remains unclear, an interaction between sodium channel–blocking drugs and an abnormal substrate (eg, ischemia or scar), resulting in slow conduction and reentrant ventricular arrhythmias, is one likely mechanism on the basis of available experimental and clinical observations.

Genetic factors may also play a role in determining susceptibility to the conduction-slowing effects of sodium channel–blocking drugs. Recently, investigators demonstrated that an SCN5A promoter polymorphism common in Asians modulates the duration of the PR and QRS intervals, important indexes of cardiac conduction. Furthermore, the study found that the extent of QRS widening after challenge with sodium channel–blocking drugs was genotype dependent, with a clear gene-dose effect evident in the study population. These observations raise the possibility that genetic variants in sodium channel expression may, in some
populations, account for a significant portion of the phenotypic variability in the QRS interval and may modulate responses to stressors such as sodium channel–blocking drugs, ischemia, and congestive heart failure. These stressors, alone or in combination, may in turn predispose individuals with the most vulnerable genetic and anatomic substrates to the risk of ventricular arrhythmias and sudden death. Although this hypothesis remains to be tested, it is clear that individuals vary in their ability to maintain sodium channel function and that this variability is explained, at least in part, by genetic factors.

Class I antiarrhythmic drugs such as those studied in CAST have the greatest tendency to block sodium channel activity and induce proarrhythmia. However, a wide variety of other agents, including local anesthetic agents, anticonvulsants such as phenytoin, tricyclic antidepressants, and drugs used to treat neuropathic pain, diabetes, and immunomodulators, as well as many others, can also exhibit sodium channel blockade at pharmacological doses. As is true for HERG inhibition and QTc prolongation, the greatest individual proarrhythmic risk related to sodium blockade is associated with the use of antiarrhythmic drugs, but the greatest population risk likely resides in the use noncardiac drugs, which are far more widely prescribed.

In addition to slowing of conduction velocity, particularly in ischemic or injured tissue, sodium channel–blocking drugs may also selectively abbreviate epicardial action potential duration, resulting in a transmural gradient of repolarization, elevation of the ST segment, and reentry. This effect has become evident in the unmasking or exacerbation of the Brugada syndrome, a disorder related to genetic defects in the cardiac sodium channel, by sodium channel–blocking drugs. Initial reports described ST elevation in the right precordial leads, typical of Brugada syndrome, in patients exposed to class 1C antiarrhythmic drugs that have potent sodium channel–blocking properties. More recently, monitored administration of drugs such as amlodine and flecainide has come into routine clinical use as a diagnostic tool in the evaluation of patients with borderline or suspected ECG manifestations of the Brugada syndrome. Lithium has similarly been found to be capable of unmasking the Brugada syndrome through sodium channel blockade, an effect that has also been seen with other noncardiac drugs, including tricyclic antidepressants, fluoxetine, first-generation antihistamines, α-adrenergic blocking agents, propofol, and cocaine. Interestingly, lithium was discovered to block cardiac sodium channels only after it was found to unmask the Brugada syndrome in patients. Recently, a mutation in SCN5A has been described that predisposes to ventricular tachycardia in the presence of class I drugs such as lidocaine.

The vast majority of patients receiving antiarrhythmic drugs that act predominantly through sodium channel blockade are selected on the basis of a low-risk profile for proarrhythmia (eg, absence of ischemic or other structural heart disease) and are generally monitored with routine ECGs, which are likely to detect evidence of excessive sodium channel blockade, manifest as widening of the QRS complex. In contrast, patients treated with noncardiac drugs that have sodium channel–blocking properties are less likely to have such screening. In the large majority of patients, this will have no untoward sequelae. However, in a small subset of vulnerable patients predisposed to arrhythmia by genetic or acquired factors such as myocardial ischemia or infarction, these agents may, under some conditions, pose a risk of potentially life-threatening proarrhythmia. Interestingly, the Cardiac Arrhythmia Pilot Study (CAPS; a precursor to CAST) evaluated the tricyclic antidepressant imipramine in addition to the classic antiarrhythmic agents encainide, flecainide, and moricizine, because imipramine is also a sodium channel–blocking agent that can suppress ventricular ectopy. Imipramine did suppress ventricular ectopy in CAPS but to a lesser degree than the other agents, so it was not included in CAST. Further evidence of the clinically relevant sodium channel–blocking property of tricyclic antidepressants is given in a case report describing a Brugada ECG pattern resulting from desipramine administration, which could pose an arrhythmic risk in a vulnerable patient. Additionally, use of tricyclic agents has been associated with increased overall mortality. The precise mechanism responsible for this mortality increase with tricyclic antidepressants has not been elucidated but could relate, at least in part, to proarrhythmic effects resulting from their sodium channel–blocking properties.

Examples of proarrhythmia induced by sodium channel–blocking drugs are not commonly identified in clinical practice. Although these events may indeed be rare, it is also possible that they are largely undetected. Unlike TdP resulting from QT-prolonging drugs, the ventricular arrhythmias induced by sodium channel–blocking drugs do not have a unique ECG signature that allows them to be readily identified and distinguished from other forms of ventricular tachycardia or fibrillation. Although forms of ventricular tachycardia with markedly widened QRS complexes and a sine-wave morphology may occur with sodium channel toxicity, they may also occur in patients with hyperkalemia, severe diffuse ischemia, or advanced left ventricular dysfunction and heart failure. Thus, it may be impossible to distinguish drug-induced proarrhythmia in these settings on the basis of ECG phenotype. Furthermore, the results of CAST suggest that patients who experience sodium channel–induced proarrhythmia are likely to die suddenly or to present with cardiac arrest rather than syncope or self-terminating ventricular tachycardia as is commonly seen with drug-induced TdP.

**Current Strategies to Reduce Drug-Associated Arrhythmia**

Drug-induced proarrhythmia is a problem faced by all clinicians who prescribe drugs and extends far beyond the realm of the cardiologist and cardiac electrophysiologist. As the number of available drugs expands, the potential for patients to be prescribed drugs with proarrhythmic potential, either alone or in combination with other drugs, continues to increase. Despite this reality, the level of awareness of the proarrhythmic potential of many drugs, particularly noncardiac drugs, is often low or even nonexistent on the part of the prescribing clinicians. The goal for the clinician must be to maximize the therapeutic potential of available drugs while minimizing the potential for proarrhythmic risk. For thera-
Available strategies for reducing the risk of drug-induced proarrhythmia include the exclusion by regulatory agencies of drugs with unfavorable risk-to-benefit profiles and the use of educational efforts directed at clinicians through product labeling and other educational venues and at patients through patient information packages. Warnings in product labeling are critically important, but their ability to prevent the inappropriate use of drugs in high-risk patients or in potentially dangerous combinations with other drugs is limited. A recent study reported that among hospital inpatients with a documented long QTc interval at baseline, 37.8% were prescribed a QTc-prolonging medication during the hospitalization, and only 8% of these had a repeat ECG within 48 hours of receiving the medication. Clinician education and awareness of the proarrhythmic potential of noncardiac drugs are critically important components of drug safety but alone are not adequate safeguards against the risks posed by these agents.

Computer-assisted strategies offer the potential for another important line of defense for clinicians against the proarrhythmic and other risks of the drugs they prescribe. At the simplest level, this involves the online availability of detailed descriptions of drugs with potential proarrhythmic risk, including the specific labeling for each drug, and the availability of aggregate lists of drugs with potential for QTc prolongation, available on the Arizona Center for Education and Research on Therapeutics website (http://www.azcert.org). Increasingly sophisticated computer-based systems will warn clinicians about proarrhythmic risks of drugs, even in situations in which the clinician is not aware of that risk. Electronic prescribing will allow computer algorithms to automatically alert prescribers to the dangers of various combinations of drugs, including the use of multiple agents with potential for QTc prolongation or agents that may affect the metabolism of QTc-prolonging drugs. In 1 study of computer-based alerts associated with cisapride, these alerts reduced the rate of potentially dangerous drug combinations by 66%. More sophisticated computer algorithms may ultimately allow adjustments for risk amplifiers to stratify the arrhythmic risk for individual patients and to guide clinicians away from the use of high-risk agents and toward the use of lower-risk alternatives when available. Some of the variables that might be used in this risk stratification approach include patient age, gender, body mass index, electrolyte abnormalities, concomitant drugs, and assessments of cardiac, renal, and hepatic function.

Regulatory agencies responsible for the drug approval process face the difficult challenge of determining which drugs with some known or theoretical potential for proarrhythmia should be approved for clinical use and what labeling or prescribing restrictions are appropriate to best manage this risk. This challenge is compounded by the rarity of noncardiac drug–induced proarrhythmia and the often impossible task of determining with confidence whether a true signal of cardiac risk is present in a drug development program. If regulatory agencies are too restrictive, they run the risk of withholding from clinical use drugs that may offer substantial benefit to patients at an acceptably low risk. If they are insufficiently restrictive, then considerable patient harm may result from injudicious or inappropriate use of drugs with true proarrhythmic risk. The assessment of benefit-to-risk ratios is a challenging and imprecise science, and the approval process must continue to be guided by the established criteria for efficacy and safety, as well as the nature of the therapeutic target and availability (or lack thereof) of safe and effective alternative treatment options. Drugs for benign symptomatic conditions are likely to face a more restrictive regulatory approval process than drugs that show efficacy for life-threatening conditions, particularly those for which an unmet need for treatment options exists, despite the fact that both drugs might carry some proarrhythmic risk. Other drugs already in widespread clinical use such as thioridazine and droperidol may require relabeling to warn of the presence of proarrhythmic risk when it is recognized long after drug approval. Some drugs with substantial proarrhythmic risk such as dofetilide may be deemed to offer sufficient patient benefit to warrant approval but may require restricted distribution to subspecialists, formal clinician education and certification, and inpatient initiation of therapy in a monitored setting to manage the potential for drug-induced proarrhythmia. Finally, drugs such as terfenadine, astemizole, mibefradil, terodiline, and cisapride may be withdrawn from the market if evidence of proarrhythmic risk is determined to outweigh the benefits of the drug compared with alternative agents in the same therapeutic class, even if the absolute level of proarrhythmic risk is orders of magnitude lower than that of approved antiarrhythmic drugs.

Initial evaluation of a new chemical entity for QTc-prolonging effects typically involves in vitro assessment for interaction with HERG and may include assessment of action potential effects in Purkinje or ventricular muscle fibers and QTc effects on surface ECG in intact animal models. Depending on the results of these preclinical (as well as early clinical) studies, additional investigations may be carried out in in vitro and in vivo experimental animal models to assess the effects on transmural dispersion of refractoriness in ventricular muscle, as well as induction or prevention of early afterdepolarizations and ventricular arrhythmias, compared with 1 or more active controls in a variety of models that are sensitive to drug-induced proarrhythmia. Early human studies of the drug typically involve a “thorough QT/QTc study” with the goal of determining whether the new chemical entity prolongs the QTc interval and, if so, whether the effect is dose and concentration dependent. Drug effects on the QT/QTc and other ECG intervals are typically studied at therapeutic and supratherapeutic doses in healthy volunteers early in the development program, although in some cases the thorough QT/QTc study may be carried out later in the program and, depending on the tolerability and toxicity of the drug, in a target population rather than healthy subjects. Thorough QT/QTc studies typically involve at least 2 doses (therapeutic and supratherapeutic) of the drug in question, as well as a placebo and an active control with known QTc-prolonging effects, to demonstrate sufficient sensitivity to detect QTc changes in the range of ≈5 milliseconds. A negative thorough
QT/QTc study is one in which the upper bound of the 95% 1-sided confidence interval for the largest time-matched (placebo-corrected) mean effect of the drug on the QTc interval is <10 milliseconds.\textsuperscript{75} When the largest time-matched difference exceeds the 10-ms threshold, the study is called positive. A positive thorough QT/QTc study will almost always result in a requirement for expanded ECG monitoring and safety evaluation during later stages of drug development. It should be noted that most clinical development programs are typically not large enough to determine the proarrhythmic potential of a drug with modest QT-prolonging effects, and postapproval surveillance is essential to more fully assess this risk. In some instances, sponsors have carried out large postmarketing clinical trials to address the theoretical risk of excess mortality associated with modest degrees of drug-induced QTc prolongation.\textsuperscript{76} With other drugs such as atypical antipsychotics or the combined use of erythromycin with cytochrome P-450 3A inhibitors, objective assessment of the clinical risk of SCD has required the use of a large simple trial design or large-scale pharmacoepidemiological studies from extensive clinical payor databases.\textsuperscript{29,77}

**Future Strategies**

Future strategies to reduce the arrhythmic risk posed by drugs will take many forms. Molecularly targeted modification of drugs will become increasingly feasible to retain the desirable properties of therapeutic agents while avoiding undesirable cardiac electrophysiological properties such as QTc prolongation. A greater understanding of the interaction of drugs with relevant structures such as the HERG channel\textsuperscript{30} will greatly facilitate this process.

Genetic differences between individuals will also likely play an increasingly important role in the future in assessment of individual arrhythmic risk. At the present time, this is evident primarily in patients known to have a heritable form of LQTS or Brugada syndrome. These patients and their physicians are typically aware of the need to assess the risks of and alternatives to any drug with the potential for prolonging the QTc or QRS intervals. In the future, this may expand to subclinical forms of LQTS and Brugada syndrome that can be detected by genetic screening but not by ECG analysis, as well as a variety of other genetic variants that can affect the pharmacokinetics or pharmacodynamics of these drugs. Experimental models of the effects of anesthetic drugs on transgenic LQT1 and LQT2 demonstrated differing effects of these drugs on arrhythmias based on the genetic phenotype.\textsuperscript{78} Ultimately, this genetic information may become part of computer-based approaches to the assessment of individual risk for drug-induced proarrhythmia.

In the future, there may be a place for drugs designed or used specifically to reverse the proarrhythmic potential of other drugs or genetic conditions. Agents with the potential to shorten the QTc interval have been developed, although they have not yet been approved for clinical use and their safety and efficacy remain to be established. A chemical that activates HERG and thereby shortens the QTc has been described,\textsuperscript{79} although it should be noted that both the genetic LQTS and short-QT syndromes can be associated with fatal arrhythmias and therefore the clinical benefit-to-risk ratio of such an agent may be difficult to define. Of note, the risk of proarrhythmia from drug-induced QTc shortening remains a theoretical risk that, to the best of our knowledge, has not been documented in the clinical setting. Recently, 2 different HERG activators were shown to reduce action potential duration and early afterdepolarizations in response to sea anemone toxin ATX-II, a mimic of LQT3.\textsuperscript{80} It is conceivable that these agents could reduce the arrhythmic risk for patients with genetic LQTS and reduce the risk of QTc-prolonging medications when coadministered. Inhibition of the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger has been recently shown to reduce action potential duration, early afterdepolarizations, and TdP in the setting of both HERG-blocking and SCN5A-activating drugs (mimicking LQT2 and LQT3, respectively).\textsuperscript{81} Other examples of beneficial drug effects include reports suggesting that quinidine may ameliorate the ECG phenotype and arrhythmic risk of patients with Brugada syndrome via quinidine-induced I\textsubscript{Kr} blockade\textsuperscript{82,83} and may effectively treat (by I\textsubscript{Kr} blockade) the gain-of-function mutation in I\textsubscript{Kr} associated with 1 form of the congenital short-QT syndrome,\textsuperscript{84} as well as the use of mexiletine or flecainide as a treatment for congenital LQT3.\textsuperscript{85–87}

**Conclusions**

Our understanding of drug effects on cardiac depolarization and repolarization and the resulting potential for proarrhythmia has increased markedly since the initial descriptions of syncope and SCD associated with drugs such as quinidine. It is now clear that there is a close association between genetic and acquired forms of the LQTS, and in any given patient, the QTc interval and susceptibility to drug-induced proarrhythmia are determined by both genetic and acquired factors. As our understanding of these phenomena has grown, so has the complexity of managing the proarrhythmic potential of drugs in an era of polypharmacy and drug-drug interactions in patients with multiple comorbidities and risk factors for arrhythmia. Currently, awareness of the proarrhythmic potential of noncardiac drugs, combined with computer assistance when drugs are prescribed and dispensed, can help mitigate this risk. In the future, improved computer algorithms, along with increasingly sophisticated genetic profiling, will help clinicians identify vulnerable patients and minimize the potential for noncardiac drug-induced proarrhythmia.

**Disclosures**

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