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Drug-induced Inhibition and Trafficking Disruption of ion Channels: Pathogenesis of QT Abnormalities and Drug-induced Fatal Arrhythmias

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Abstract: Risk of severe and fatal ventricular arrhythmias, presenting as Torsade de Pointes (TdP), is increased in congenital and acquired forms of long QT syndromes (LQTS). Drug-induced inhibition of K^+ currents, IKs, IKr, IK1, and/or Ito, delay repolarization, prolong QT, and increase the risk of TdP. Drug-induced interference with IKr is the most common cause of acquired LQTS/TdP. Multiple drugs bind to KNCH2-hERG-K^+ channels affecting IKr, including antiarrhythmics, antibiotics, antivirals, azole-antifungals, antimalarials, anticancer, antiemetics, prokinetics, antipsychotics, and antidepressants. Azithromycin has been recently added to this list. In addition to direct channel inhibition, some drugs interfere with the traffic of channels from the endoplasmic reticulum to the cell membrane, decreasing mature channel membrane density; e.g., pentamidine, geldalamicin, arsenic trioxide, digoxin, and probucol. Other drugs, such as ketoconazole, fluoxetine, norfluoxetine, citalopram, escitalopram, donepezil, tamoxifen, endoxifen, atazanavir, and roxitromycin, induce both direct channel inhibition and impaired channel trafficking. Although many drugs prolong the QT interval, TdP is a rare event. The following conditions increase the risk of drug-induced TdP: a) Disease states/electrolyte levels (heart failure, structural cardiac disease, bradycardia, hypokalemia); b) Pharmacogenomic variables (presence of congenital LQTS, subclinical ion-channel mutations, history of or having a relative with history of drug-induced long QT/TdP); c) Pharmacodynamic and kinetic factors (high doses, women, elderly, metabolism inhibitors, combining two or more QT prolonging drugs, drugs that prolong the QT and increase QT dispersion, and drugs with multiple actions on ion channels). Because most of these conditions are preventable, careful evaluation of risk factors and increased knowledge of drug use associated with repolarization abnormalities are strongly recommended.

Keywords: drug-induced arrhythmia, channel trafficking, long and short QT, Torsade de Pointes, potassium channels.

INTRODUCTION

Drug-induced ventricular arrhythmia is an infrequent but sometimes fatal event [1]. Although expected for antiarrhythmic drugs interfering with potassium channels (Class III drugs), many non-antiarrhythmic drugs have shown proarrhythmic activity, presenting as a ventricular polymorphic tachycardia described as Torsade de Pointes (TdP) [1-6]. TdP may manifest as palpitations, syncope, seizure-like activity, cardiac arrest requiring resuscitation, and/or as sudden cardiac death [1-5]. The severity of the outcomes has led to the removal from the market of some antibiotics, prokinetics, antihistaminics and antipsychotics [7]. It has been estimated that TdP occurs in 4 out of 100,000 individuals per year, but a higher rate is expected in predisposed patient groups [8]. The absence of ECG data for most cases of sudden death makes it impossible to document TdP as the culprit. Therefore, both cardiovascular mortality and cardiac sudden death have been employed as indicators of drug-induced severe and fatal arrhythmias.

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TdP is commonly associated with a prolonged QT interval (long QT syndrome, LQTS). Long QT may result from either congenital or acquired mechanisms. Drug-induced long QT is by far the most common, and hence, preventable cause of long QT. Updated information about drugs associated with increased risk of TdP may also be found at www.crediblemeds.org. Other predisposing factors for TdP are repolarization heterogeneity, electrolyte abnormalities, and structural cardiac disorders [5, 9, 10]. Coexistence of predisposing factors increases the likelihood of developing TdP. Silent mutations of cardiac ion channels are responsible for many cases of drug-induced long QT syndrome, TdP and/or sudden death, despite having normal QT duration on the resting ECG [11, 12].

ION CHANNELS, QT INTERVAL, QT HETEROGENEITY, REPOLARIZATION RESERVE AND VENTRICULAR ARRHYTHMIAS

The action potential of ventricular cardiac muscle results from a coordinated activation and deactivation of ion channels (Table **1**). Sodium entry via Nav1.5 channels determines the phase 0 of the action potential. This is followed by a rapid partial repolarizing K^+ current (Ito) through Kv4 channels producing the notch of the action potential. Next, a combination of calcium (Cav 1.2 channels) and sodium entry, and of potassium exit via IKr and IKs currents, deter-

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Table 1. Main cardiac ion currents involved in QT abnormalities: Genes, Channels, LQTS and SQTS.

Gene-α subunit	Gene- β subunit	Current name	Repolarization	Loss of Function	Gain of Function
KCND3-Kv4.3	KChIP2.2	Ito, f Transient outward or rapid partial repolarizing	Notch of the action potential		SQTS Brugada
KCNQ1-KvLQT1-Kv7.1	KCNE1/Mink	IKs Slowly activating delayed rectifier	Repolarization	LQTS1 LQTS + reactive hypoglycemia + low serum K^+	SQTS1
KCNH2/hERG-Kv11.1	KCNE2/MiRP1	IKr Rapidly activating delayed rectifier	Repolarization	LQTS2	SQTS2
KCNJ2- Kir2.1		IK1 Inwardly rectifying	Terminal phase diastolic membrane potential/maintains negative resting potential	LQTS Andersen-Tawil syndrome	SQTS3
SCN5A-Nav1.5	SCN1B-Navβ1	Nav1.5	Fast depolarization (phase 0) of the action potential,	Brugada	LQTS3

mine the plateau period. The late sodium current (INa-L) is the small sodium channel current that persists throughout the plateau of the cardiac action potential. IKs, the slowly activating delayed rectifier K^+ current, and the rapidly activating delayed rectifier potassium current, IKr, constitute the main repolarizing currents [13, 14]. A final potassium current, known as the inward rectifier potassium current (IK1 current), becomes activated during the late part of the repolarization and plays a role in maintaining the negative resting potential (phase 4).

The width of the ventricular action potential determines the duration of the QT interval of the ECG. QT interval duration varies from beat to beat, shows circadian variation, and is affected by gender and changes in the heart rate and in autonomic tone. The faster the heart rate the shorter the QT interval; consequently, a rate corrected QT (QTc) is commonly employed [15, 16]. QTc values greater than 450 msec for men and greater than 470 msec for females are usually considered as abnormally prolonged intervals [16, 17]. QT interval variation in general population is largely heritable [17, 18].

Long QT is associated with increased risk of TdP and sudden death [19-23]. Interference with the IKr is the most common mechanism of congenital and drug-induced triggered arrhythmias associated with long QT [19-21]. When the period of repolarization is prolonged (long QT), depolarizing currents (after-depolarizations) may ensue, which when repeated and of sufficient magnitude, trigger ventricular arrhythmias. TdP is classically associated with early-afterdepolarizations, defined as depolarizing currents occurring early during the period of repolarization [24, 25]. Early-afterdepolarizations commonly result from inward calcium currents. By increasing membrane L-type calcium channels, sympathetic stimulation and administration of beta-receptor agonists increase risk of TdP in the presence of prolonged repolarization. In addition to long QT, QT dispersion or variability of QT also predicts risk of TdP [8, 26, 27], and of cardiac mortality in the general population and in diabetics [28-30]. Agents that prolong the QT interval but fail to increase the transmural dispersion of repolarization (TDR) are moderately effective in inducing TdP [26, 27, 31]. QT dispersion is indicative of heterogeneity of repolarization times in the ventricular cardiac muscle. Differences in the speed of repolarization of the cell layers of the ventricles may produce transmural voltage gradients and heterogeneity of repolarization rates. QT dispersion is commonly estimated from the difference between the maximum and the minimum QTc in any thoracic lead. Values greater than 80 msec indicate excessive dispersion of repolarization. In summary, ECG assessments of increased risk of TdP should include: QT interval duration, beat-to-beat QT variability (QT dispersion), time interval from peak to the end of the T wave, presence of T-wave alternant (change in amplitude or polarity of T wave on alternating beats), morphology of the T waves, and presence of "T-U waves" [20, 26, 27, 31-33].

GENES AND POTASSIUM ION CHANNELS

Ion channels are constituted of alpha-subunits, which complex with beta-subunits and other proteins that regulate channel function and kinetics (Table **1**). Beta-subunits are important modulators of the pore-forming alpha-subunits. IKs alpha-subunit channel protein is known as KvLQR1 (Kv7.1) and is encoded by the KCNQ1 gene; its beta-subunit, known as KCNE1 or Mink, is encoded by the KCNE1 gene. The alpha-subunit for the channel responsible for IKr current is known as hERG (Kv11.1) and is encoded by the KCNH2 gene. HERG coassembles with a beta-subunit known as KCNE2 (or MiRP1) encoded by KCNE2 gene. However, there is controversy on whether KCNE2 (MiRP1) is the only beta-subunit of hERG and if such subunit may be exclusive for the IKr channels [34-36]. It has been shown that KCNE2 is able to bind and regulate most K^+ channels including the pacemaker currents (IKf). In addition, IKs beta-subunit can form stable complexes with hERG to

increase IKr current [37, 38], and mutations in IKs beta-subunit may affect hERG function [36, 39, 40]. These findings are supported by the clinical observation of a patient carrying an A8V KCNE1 mutation presenting as LQTS with no changes in IKs, but reduced IKr/hERG current [41]. To add to the complexity, KCNQ1 has also been shown to modulate hERG function by enhancing membrane expression of hERG [42].

ION CHANNELS AND CONGENITAL FORMS OF LONG QT SYNDROME (LQTS)

Ion channel mutations may alter channel opening and closing (i.e., gating), channel location (trafficking), anchoring, and its interactions with cytoskeletal proteins. Some mutations lead to loss of function, whereas others lead to gain of function (Table **1**). Congenital LQTS is commonly described as QT prolongation due to delayed repolarization, associated with increased risk of TdP, which may present as syncope, seizures and sudden cardiac death. It usually presents in otherwise healthy young individuals with no structural heart disease [1]. In the absence of ischemic heart disease, congestive heart failure, cardiomyopathies, marked bradycardia, electrolyte abnormalities (low potassium and low magnesium), acidosis, subarachnoid hemorrhage, human immunodeficiency virus disease [43], or drug therapy, the presence of an abnormally prolonged QTc interval is suggestive of congenital LQTS [31, 44, 45]. Mutations in genes coding for ion channel alpha-subunits cause most cases of congenital LQTS [46-48]. Mutations on genes coding for beta-subunit proteins appear to have less effect on ion currents, not necessarily increasing the duration of the QT interval on the resting ECG [35]. However, these individuals may still be prone to developing LQTS and ventricular arrhythmias when exposed to hERG blockers, and have been labeled as having a reduced repolarization reserve [49].

Nearly 80% of congenital LQTS are observed in individuals with defects in genes encoding for the alpha-subunits of the following ion channels: KCNQ1-encoded-IKs (LQTS1), KCNH2-encoded IKr (LQTS2), and SCN5A-encoded INa (LQTS3). LQTS1 and LQTS2 are determined by loss of function mutations that lead to reduced IKs and IKr currents, respectively, prolonging repolarization time (Table **1**). Defective KVNH2/hERG channel trafficking seems responsible for the loss of function associated with LQTS2 mutations [50, 51]. Hyperinsulinemia, clinically relevant symptomatic reactive hypoglycemia, and decreases in serum potassium following an oral glucose challenge, have been described in some patients with LQTS1.

LQTS3 is characterized by a gain of function mutation at the SCN5A-encoded INa. The delayed incorporation of sodium channels to the cell membrane (non-inactivating sodium current) leads to late-sustained depolarizing currents prolonging repolarization, the action potential and the QT interval [52]. This condition is associated with afterdepolarizations, triggered arrhythmias, and automaticity [53]. In LQTS3, arrhythmia-related events occur most frequently at rest or during sleep. On the other hand, in LQTS1, arrhythmias are commonly triggered by exercise and swimming; whereas, auditory stimuli commonly trigger life-threatening arrhythmias in LQTS2.

In addition, to the above described most common forms of the LQTS, other mutations may also lead LQTS (Table **1**). Loss and gain of function mutations and drug effects on IK1 channels may affect QT duration, and increase risk of arrhythmias. The KCNJ2 gene encodes the alpha-subunit of the potassium channel Kir2.1, which is responsible for the IK1 current (Table **1**). Loss of function KCNJ2 mutations lead to long QT, large U waves, frequent PVCs, and a special type of polymorphic ventricular tachycardia known as bidirectional ventricular tachycardia. When the loss of function KCNJ2 mutation presents with dysmorphic features and periodic paralysis is known as the Andersen-Tawil syndrome [54, 55]. The arrhythmic episodes are increased by low K^+ and beta-receptor stimulation [56, 57]. Gain-of-function mutations increasing IK1 (E299V mutant) produce the SQTS3 (QTc interval $\leq$330 ms), often associated with paroxysmal atrial fibrillation (Table **1**). Use of IK1 agonists (zacopride) and antagonists (dronedarone and chloroquine) for the treatment of these syndromes awaits further investigation [58] (Table **2**).

DEFECTIVE ION CHANNEL TRAFFICKING AS CAUSE OF LQTS: MECHANISMS AND DRUG EFFECTS

Mutations in potassium channel genes may delay repolarization by either producing dysfunctional channels and/or by decreasing the density of mature channels on the cell membrane. The latter may result from defective trafficking of the channels from the endoplasmic reticulum to the cell membrane. Abnormal channel folding, retention at the endoplasmic reticulum, defective chaperones, and/or increase proteasomes activity, may be involved in defective trafficking [59, 60]. Assembled channels are normally synthesized and integrated into the endoplasmic reticulum and, after correct folding, are trafficked to the cell surface. Channel misprocessing and/or abnormal channel trafficking affect the number of mature channels on the cell membrane affecting ion currents [59, 60]. Trafficking disruption of hERG channels is commonly assessed by measuring the ratio of the expression of mature hERG (155 kDa) at the cell membrane, to immature (135 kDa) hERG, located in the endoplasmic reticulum. Increases in immature hERG channels in the endoplasmic reticulum and decreases in membrane mature hERG, are indicative of altered channel trafficking [61, 62]. The chaperones, Hsp90 and Hsp70, interact directly with the core-glycosylated form of hERG present in the endoplasmic reticulum. These chaperones are essential for the maturation of hERG channels and for retaining abnormal mutants. Decreased expression of Hsp90 and reduced interaction with hERG suggest that trafficking inhibition is due to reduced channel folding. Abnormally folded channels activate the unfolded protein response, and the immature channel is ubiquitinized and then degraded in lysosomes and proteasomes [62]. Inhibition of Hsp90 chaperone prevents maturation and increases proteasomal degradation of hERG, reducing the number of mature channels available to be incorporated into the cell membrane. Similarly defective chaperone systems are associated with reduced membrane channel density.

LQTS2 results from hERG N470D and hERG R752W channel mutations. These mutations lead to defective hERG

Table 2. Drugs with activity on cardiac potassium channels.

K^+ current	Inhibition	Stimulation
Ito,f	4-aminopyridine, haloperidol, dapoxetine, duloxetine, fluoxetine, trazodone, mozapride, raloxifene, rosiglitazone, ranolazine, sibutramine, trifluperazine, diltiazem, candesartan, eprosartan; bupivacaine; ropivacaina, tedisamil	β1-receptor stimulation;
IKs	MT2-2 peptide from scorpion BmKTX toxin [152]; SjAPI-2 nurotoxin [153]; chlorthalidone; fluoxetine, norfluoxetine [154], quinidine, amiodarone, azimilide, HMR-1556; chromanol293B [155].	β1-receptor stimulation; stilbenes-fenamates.
IKr	Antiarrythmics with Class III activity, Antibiotics (fluoroquinolones, macrolides), Azole Antifungals (ketoconazole), Antimalarials (chloroquine), Antipsychotics (phenothiazines, butyrophenones), Antidepressants (TCAs, SSRIs), Anticancer (arsenic trioxide, anthracyclines, VEGFI-TKI), Antiviral (atazanavir), 5-HT3 antagonists (ondansetron), Anti-migraine (5-HT1B/1D receptor agonists), Prokinetics (cisapride), anti-estrogens (tamoxifen), PDEIII inhibitors (cilostazol), Papaverine, others	β1-receptor stimulation
IK1	dronedarone, chloroquine, M2 cholinergic agonits,	β1-receptor stimulation; zacopride

Inhibition of IKr currents have been studied more extensively and are suitable to inhibition by many more agents than the other K^+ currents. For IKr currents, one or two prototype drugs where provided for each class. Detailed information is found on the text of the manuscript.
VEGFR: vascular endothelial growth factor receptor.
TKI: tyrosine kinase inhibitory activity
TCA: tricyclic antidepressants
SSRI: Selective serotonin reuptake inhibitors
PDE III: phosphodiesterase III inhibitors.

channel trafficking, decreased number of mature channels on the cell membrane, slower IKr, prolonged repolarization and long QT [61-65]. Astemizole and cisapride were shown to rescue functional channel proteins for hERG N470D mutations by dissociating the channels from the chaperones (43). Nevertheless, its clinical use is limited because both drugs are more effective as channel blockers than as channel trafficking stabilizers [45, 64]. N-[N-(N-acetyl-l-leucyl)-l-leucyl]-l-norleucine was shown to correct the diminished IKr currents present in cells carrying A561V missense mutation in the hERG alpha-subunit. This mutation is characterized by changes in the expression of folding chaperones and processing proteasomes leading to retention of hERG in the endoplasmic reticulum [66]. Recently, a selective sodium channel toxin acting at the endoplasmic reticulum was found to rescue mutations of the voltage gated sodium channel Na(V)1.1 (SCN1A) [67]. In summary, selective ion channel rescue agents, chaperones, and drugs acting at the endoplasmic reticulum or at the channel degradation system, may help in the treatment of congenital LQTS resulting from impaired channel trafficking [65].

USE OF QT-PROLONGING DRUGS FOR THE TREATMENT OF THE SHORT QT SYNDROME

Short QT syndrome (SQTS) is a new genetic disorder associated with a high rate of familial sudden death [68, 69]. The ECG is characterized by a very short QT interval (<320 milliseconds), almost no ST segment, and tall, peaked, narrow-based T waves, due to shortening of atrial and ventricular refractory periods. There is a marked propensity for paroxysmal atrial fibrillation, and increased risk for sudden cardiac death from ventricular tachyarrhythmia. Gain of function mutations in K^+ channels characterize the most common forms of SQTS; e.g., SQT1 (IKs), SQT2 (IKr) and SQT3 (IK1) (Table **1**). These mutations lead to an increase in the IK currents (IKr, IKs, and IK1) shortening the action potential and the QT interval. Although an implantable cardioverter defibrillator is often the therapy of choice, pharmacological treatment with QT prolonging drugs has also been used. In patients carrying a mutation in the IKr-coding gene KCNH2 (hERG), quinidine was found more effective than sotalol and ibutilide in prolonging the QT interval and normalizing the effective refractory periods [68]. The superiority of quinidine to class IC and Class III drugs was confirmed in another study [69], where hydroquinidine was found to prolong the QT interval from 263 +/- 12 ms to 362 +/- 25 ms, and to prevent inducibility of ventricular fibrillation. Therefore, drugs known to prolong the QT interval and in particular quinidine, can be effective in the treatment of SQTS. A review of the treatment of SQTS was recently published [70].

The KV4.3 alpha-subunit encoded by KCND3 and the KChIP2 beta-subunit are responsible for the cardiac fast transient outward K^+ current (Ito,f), also known as early repolarization of the action potential (notch on the action potential) (Table **1**). Gain of function mutations of KCND3 may also lead SQTS (Table **1**). Two human mutations (G600R and L450F) in KV4.3 are associated with Brugada's syndrome. These mutations are characterized by increases in the fast transient outward K^+ current (Ito,f). [71]. Haloperidol, dapoxetine, duloxetine, fluoxetine, trazodone, mozapride, raloxifene, rosiglitazone, ranolazine, sibutramine, trifluperazine, diltiazem, candesartan, and eprosartan inhibit KV4.3 currents [72] (Table **2**). Their use in the treatment of gain of function KV4.3 mutations is under investigation.

ACQUIRED LQTS: DRUG-INDUCED QT PROLONGATION AND INCREASED RISK FOR TORSADES DE POINTES

Most cases of drug-induced long QT result from an action of the drugs on the ion channel proteins encoded by the hERG gene that is responsible for the IKr repolarizing current (Table **2**). Drug-induced QT prolongation is commonly achieved by directly blocking the hERG channel. In addition, disruption of channel trafficking may decrease the number or the rate of incorporation of mature potassium channels into the cell membrane [22, 44] (Table **3**). Arsenic trioxide, ketoconazole, fluoxetine, citalopram, escitalopram, norfluoxetine, donepezil, atazanavir, roxithromycin, tamoxifen and endoxifen have been shown to prolong the QT interval by a combination of direct channel blockade and inhibition of channel trafficking (Table **3**). The large number of aromatic residues present in the hERG potassium channel, compared to other ion-channels, may account for its high susceptibility to inhibition by a variety of structurally different agents [65]. The hydrophobic central cavity of the hERG K^+ channels may stabilize the binding of drugs to the channel proteins leading to IKr inhibition [65]. As a consequence of the large number of structurally different drugs with inhibitory properties on the function of hERG potassium channels/IKr currents, all new therapeutic entities require extensive preclinical screening.

Although many drugs inhibit the IKr, fortunately only very few patients develop TdP when treated with QT- prolonging drugs [5]. The low incidence and often-unpredictable emergence of TdP may result from individual differences in pharmacogenomics, disease states, electrolyte imbalances, and combined drug therapies affecting drug dynamics and kinetics. All of these factors affect the subject's repolarization reserve. The concept of repolarization reserve has been employed to account for individual differences in susceptibility to develop TdP with drugs or conditions known to affect potassium currents [5, 73]. In fact, 5-19% of people developing drug-induced TdP were found to have a low repolarization reserve due to subclinical ion-channel mutations [74]. In addition to genetic factors, drugs may exert multiple actions on cardiac repolarization and receptors, counteracting or increasing their primary effects on IKr currents [75].

Use of antiarrhythmic drugs with class III activity is associated with increased risk of TdP, an expected outcome resulting from their mechanism of action; namely, inhibition of hERG/IKr. [44, 74, 76] (Table **2**). These antiarrhythmics

Table 3. Mechanisms of drug-induced hERG-K^+ channel inhibition.

Drugs/Drug Classes	Direct inhibition of hERG K^+ channel.	Inhibition of hERG K^+ channel trafficking
Phenothiazines	+	-
Pentamidine	-	+
Geldalamicin	-	+
Ranolazine	+	-
Arsenic Trioxide	-	+
Fluoxetine, Norfluoxetine	+	+
Ketoconazole	+	+
Digitoxin, Ouabain, Digoxin	?	+
Sparfluoxacin,Ciprofloxacin, Ofloxacin	+	-
Amsacrin	+	-
Probucol	-	+
Donepezil	+	+
Tamoxifen, Endoxifen	+	+
Berberine	*?*	+
Citalopram,Escitalopram, Fluoxetine, Norfluoxetine	+	+
Atazanavir	+	+
Roxitromycin	+	+
Halofantrine,Chloroquine Mefloquine, Desbutyl-lumefantrine, Lumefantrine	+	*?*

Drug-induced inhibition of IKr currents can be achieved either by direct inhibition of potassium channels and/or by reducing the number of channels at the cell membrane. The latter is achieved by drug-induced impaired channel trafficking from the endoplasmic reticulum to the cell membrane. Data on drug-induced inhibition of channel trafficking is not available for all drugs.

Table taken with permission from Cubeddu [156]. Table content was modified and updated.

inhibit outward K^+ current, delay repolarization, prolong the QT interval and increase refractoriness. Quinidine, dofetilide and ibutilide are all associated with TdP and are potent blockers of the IKr channel; thus, for these three agents there is a strong association between long QT and TdP. Quinidine inhibits both IKs and IKr, and prolongs the duration of QT interval (Table **2**). Quinidine–induced increases in QT dispersion is greater at slow than at fast heart rates, accounting for higher risk of TdP during bradycardia.

An association between IKr blocking potency and the liability of a drug to cause TdP is not clearly observed for all antiarrhythmic drugs. Verapamil is an effective inhibitor of IKr currents [77]. However, verapamil also blocks L-type calcium channels and decreases transmural dispersion of repolarization. The combination of both actions may account for the low incidence of TdP associated with its use [74, 77]. An interesting example of class III drugs associated with TdP is sotalol [75]. Sotalol is composed of a racemic mixture of D- and L-sotalol. D-sotalol inhibits the IKr and prolongs the QT interval [78]. L-sotalol, on the other hand, is a beta-blocker. The racemic mixture has been reported to be less arrhythmogenic than the D-sotalol, possibly due to antagonism of beta-receptors induced by L-sotalol [78]. Sotalol-induced recurrent TdP has been observed in patients with end-stage renal disease, which may result from very high plasma levels of sotalol, since the drug is not adequately eliminated by renal dialysis [79]. At high concentrations, sotalol prolongs the QT interval and increases the variability of the QT interval, creating repolarization heterogeneity; further increasing the risk of developing TdP [79, 80]. Amiodarone exerts inhibitory effects on the IKr and the IKs currents, prolonging repolarization and the QT interval (Table **2**) [81]. Despite the bradycardia and the large QT prolongation associated with chronic amiodarone therapy, TdP and other drug-induced tachyarrhythmia are less frequent than expected. Amiodarone reduces the heterogeneity of repolarization across cell types within the myocardium (epi, endo and mid-myocardial cells), decreasing QT dispersion [82]. In addition, amiodarone has beta-receptor antagonistic properties and calcium channel blocking activity. These additional actions may explain the lower than expected incidence of TdP observed with amiodarone, despite QT prolongation. TdP associated with amiodarone treatment is observed more frequently in women than in men.

Cardiac glycosides are also potent inhibitors of hERG expression at the cell surface, reducing IKr currents, and prolonging repolarization and the QT interval. Digitoxin, ouabain, and digoxin seem to inhibit IKr by decreasing the density of hERG-dependent potassium channels on the cell membrane (Table **3**). The reduced number of potassium channels results from abnormal channel trafficking due to inhibition of channel release from the endoplasmic reticulum [83]. A lesser number of membrane hERG channels reduce IKr, prolonging the QT interval.

NON-ANTIARRHYTHMIC DRUGS ASSOCIATED WITH INCREASED RISK OF TdP

Although the class III antiarrhythmics were designed to prolong cardiac repolarization and increase refractoriness, for other drugs repolarization delay is an unwanted side effect. A recent study demonstrated that the risk of cardiac arrest, in hospitalized patients with several underlying diseases, was increased 2-fold with the use non-antiarrhythmic QT-prolonging drugs [84]. The risk of cardiac arrest was higher if receiving more than one daily dose, if treated with more than one QT-prolonging drug, and with drugs that interfere with the metabolism or elimination of the QT prolonging agent [84, 85]. TdP associated with intravenous drug administration generally occurred at the time of peak plasma levels [84]. Drug risk of TdP has been ranked as drugs with known risk, possible risk, and conditional risk of TdP. In addition, drugs have also been classified as drugs to be avoided in patients with congenital LQTS. Updated information may be found at www.crediblemeds.org (Table **2**).

Macrolide antibiotics may induce QT prolongation and its use is associated with risk of TdP [86, see 87 for review] (Table **2**). Erythromycin, azithromycin, clarithromycin, telithromycin and roxithromycin are listed either as drugs that are known or that are possibly linked to TdP. Greater effects on ventricular repolarization have been reported with erythromycin, in particular at high doses and during intravenous administration [88]. The following QT prolonging potency has been reported: erythromycin > clarithromycin > roxithromycin > azithromycin [89]. Erythromycin, clarithromycin, and azithromycin not only prolonged the QT interval but also increased the dispersion of repolarization [90]. Hypokalemia is a risk factor for QT prolongation and TdP in patients treated with macrolide antibiotics [87]. In addition, to their direct effect on the QT interval, erythromycin and clarithromycin exert inhibitory effects on drug metabolism by inhibiting CYP3A. A 3-fold greater incidence of sudden cardiac death was observed in patients taking erythromycin in addition to CYP3A inhibitors compared to those taking erythromycin alone [87, 91]. Combination of erythromycin with CYP3A inhibitors should be avoided and/or additional ECG monitoring is recommended. Risk of developing arrhythmias is markedly increased in patients with comorbidities, with congenital or acquired LQTS, low potassium, and women being more sensitive [92]. Sporadic missense mutations in KCNE2 leading to altered MiRP1 subunits (Q9E-MiRP1) are associated with a 3-fold greater sensitivity to inhibition of IKr by clarithromycin, increasing the risk of clarithromycin-induced TdP [35]. In addition, D76N and D85N KCNE1 (Mink) mutations also increased the *in vitro* sensitivity of IKr/hERG to inhibition by clarithromycin [36] (Table **4**). Macrolides are known to bind and inhibit the hERG channels (alpha-subunits). In addition, roxithromycin inhibits hERG channels and disrupts hERG protein trafficking [93] (Table **3**). No information was found on whether other macrolide antibiotics disrupt hERG channel trafficking.

In addition to macrolide antibiotics, the fluoroquinolone class of drugs has also been shown to induce QT prolongation and increased risk of arrhythmia [94-96, see 97 and 98 for review] (Table **2**). Levofloxacin, moxifloxacin, ciprofloxacin, gemfloxacin, norfloxacin, ofloxacin are classified as either known or possibly associated with TdP. Fluoroquinolones inhibit IKr delaying membrane repolarization [96, 99, 100]. In general, the reported relative order of potency in inhibiting IKr is: sparfloxacin > grepafloxacin > moxifloxacin = gatifloxacin > levofloxacin > ciprofloxacin > oflox-

Table 4. Reported mutations associated with changes in drug sensitivity to inhibit IKr.

Gene/subunit	Mutation	Drug	Ion Current	Effect	Ref
KCNE2 /MiRP1	Q9E-MiRP1	Clarithromycin	IKr	Increased sensitivity to inhibition	[35]
KCNE1 / Mink	D76N and D85N- Mink	Clarithromycin	IKr	Increased sensitivity to inhibition	[36]
KCNE2 /MiRP1	T8A-MiRP1	Sulfamethoxazole	IKr	Increased sensitivity to inhibition	[109]
KCNE2/SCNA/KCNE1	No mutation or polymorphisms on KCNE2-SCNA or KCNE1 were found	Risperidone	IKr	Increased sensitivity to inhibition	[124]

acin > antoflozacin. For levofloxacin, ciprofloxacin, and ofloxacin, inhibition of hERG/IKr occurred at concentrations higher than those observed clinically during treatment with these antibiotics [86, 101, 102]. The high potency in inhibiting hERG of grepafloxacin and sparfloxacin may account for the higher rate of cardiac related fatalities. For moxifloxacin, mutagenesis of the S6 helix residue Tyr652 to Ala, reduced IKr block by 66%, suggesting that the drug interacts with the channel inner cavity [103]. Fluoroquinolones-induced inhibition of hERG currents is reversible, voltage and concentration-dependent, but independent of the stimulation frequency [103]. TdP may also develop in the absence of other etiologies to cause TdP and without apparent risk factors [104].

Cardiovascular death and ventricular arrhythmia associated with macrolide and fluoroquinolone antibiotic use has been assessed in retrospective, large-scale studies. The Taiwan National Health Insurance database, a nationwide, population-based study, considered outcomes occurring within seven days after initiation of antibiotic treatment. Compared to amoxicillin-clavulanate, a drug that does not block hERG channels, use of moxifloxacin, azithromycin and levofloxacin was found to be associated with a 1 to 3 fold increase in the relative risk of cardiovascular death and ventricular arrhythmias. A second retrospective observational analysis examined 14 years of data present on the Tennessee Medicaid database [105, 106]. The study showed an increased risk of cardiovascular deaths and death from any cause during the first five days of treatment with azithromycin compared to no drug treatment or amoxicillin. When compared to non-antibiotic use (hazard ratio of 1) or treatment with amoxicillin (HR: 0.85; 95% CI, 0.45-1.60), the hazard ratio for azithromycin was significantly greater (HR: 2.71; 95% CI, 1.58-4.64). However, the absolute risk for cardiovascular events was quite low (64 sudden cardiac deaths/million treatment courses). Additional 245 deaths per 1 million courses were observed for patients with highest cardiovascular risk at baseline. In contrast, a prospective study that excluded patients with heart failure, hypokalemia, family history of LQTS, use of medications known to prolong the QT and presence of a long QT at baseline ECG, showed no differences in cardiovascular or all-cause mortality between treatment with azithromycin or placebo for one year [107].

In summary, fluoroquinolone and macrolide antibiotics should be avoided or used under ECG monitoring in subjects with congenital or acquired LQTS, in subjects treated with class Ia and III antiarrhythmics and/or with any other agent known to prolong the QT interval. Presence of ischemic heart disease, CHF, rhythm disturbances, and/or low serum K^+ increases the risk of fluoroquinolones and macrolide-induced TdP and severe arrhythmias. ECG monitoring is recommended when used in cardiac disease. Concomitant use of erythromycin and CYP3A inhibitors is associated with increased incidence of sudden death; therefore, such combination should be avoided. Women are more sensitive to the arrhythmogenic action of macrolide and fluoroquinolone antibiotics, and serum K^+ abnormalities should be corrected prior to their administration. These recommendations were recently exemplified in a patient on clarithromycin, who developed recurrent ventricular arrhythmias requiring repeated defibrillations, when placed on amiodarone and co-trimoxazole [108].

Bactrim (trimethoprim/sulfamethoxazole) has been shown to prolong the QT interval; although this is a very rare event. In a group of subjects with a previous history of drug-induced arrhythmia and normal resting ECG, a missense mutation in KCNE2 was found associated with marked QT prolongation when treated with trimethoprim / sulfamethoxazole. The resulting altered beta-subunit (T8A-MiRP1) made the IKr current very sensitive to inhibition by sulfamethoxazole [109] (Table **4**). The frequency of this polymorphism is unknown, but certainly infrequent. Therefore, due to lack of new reports of TdP associated with trimethoprim / sulfamethoxazole use, current recommendation is limited to avoiding its use in congenital LQTS or in patients with history of drug-induced LQT and TdP.

Pentamidine, an anti-protozoal and anti-fungal agent, used in the treatment of trypanosomiasis, lehismaniasis and *Pneumocistis carinii* infections, induces marked QT prolongation and arrhythmia [110, 111]. Pentamidine-induced QT prolongation results from dual inhibition of channel trafficking and reduction in membrane channel density [112] (Table 3). Geldanamycin, a benzoquinoid antibiotic, has also been shown to inhibit IKr currents by reducing trafficking of channels to the cell membrane [61] (Table **3**). By inhibiting Hsp90, geldanamycin prevents channel maturation and increases proteasomal degradation of hERG, decreasing mature membrane hERG and IKr currents [61]. Bedaquiline and delamanid (for drug-resistant tuberculosis), foscarnet, atazanavir, saquinavir and rilpivirine (anti-virals), and chloroquine, holofantrine and dihydroartemisinin+piperaquine (anti-malarials) have been associated with known or possible risk of TdP (Table **2**). Atazanavir, a HIV-1 protease inhibitor for the treatment of AIDS, prolongs the QT interval and has a known risk of inducing TdP. Atazanavir blocks hERG K^+ channels directly and also interferes with the trafficking of channels [113] (Table **4**).

The azole group of antifungals, ketoconazole, itraconazole, fluconazole, miconazole, posaconazole and voriconazole has been reported to cause important interactions with agents known to prolong the QT interval [114] (Table **2**). The azoles inhibit the hERG channel, reducing IKr. Similar to fluoxetine and norfluoxetine, ketoconazole-induced LQTS may be achieved by a combination of two effects; namely, via a direct inhibition of the potassium channel and by disrupting hERG protein trafficking [115] (Table **3**). In addition, ketoconazole, miconazole and itraconazole inhibit cytochrome P450-3A4 interfering with the metabolism of many drugs. Large increases in plasma levels may occur when azoles are combined with QT-prolonging drugs that are metabolized by this cytochrome system. Most of the deaths related to treatment with cisapride, astemizole, quinidine and terfenadine resulted from concomitant administration with azole compounds [114]. Thus, administration of two QT-prolonging drugs together with high plasma levels of one of the QT-prolonging drug increases further the risk of TdP.

Drugs used for the treatment of psychosis also share arrhythmogenic potential related to repolarization abnormalities and QT prolongation (Table **2**). A dose-dependent increased risk of sudden death was reported in current users of conventional and atypical antipsychotics [116-119]. A case-crossover study in 17718 patients, using Taiwan's National Health Insurance Research Database, showed that antipsychotic drug use was associated with a 1.53-fold increased risk of incident ventricular arrhythmia and/or sudden cardiac death [119]. A cohort study employing a Medicaid claims database in 459,614 incident antipsychotic users revealed an incidence of sudden death and ventricular arrhythmia of 3.4 and 35.1 per 1,000 person-years, respectively [120]. However, schizophrenia was also associated with increased risk of sudden cardiac death [118]; therefore, part of the drug-induced increased risk of arrhythmia may be attributable to the underlying psychiatric condition. In general, antipsychotic drugs with increased risk included clothiapine, haloperidol, levopromazine, prochlorperazine, thioridazine, mesoridazine, olanzapine, clozapine, quetiapine, risperidone, zisapridone, pamperone, paliperidone, pimozide, and sulpiride (Table **2**). Haloperidol and chlorpromazine had less favorable cardiac safety profiles than olanzapine. TdP associated with intravenous haloperidol administration was observed between 15 to 220 min of drug administration, a finding consistent with the observation of higher incidence of ventricular arrhythmias with its short-term use [121]. Of the phenothiazines tested, thioridazine was the most potent in blocking hERG channels [122, 123]. Among atypical agents, risperidone had a similar cardiac safety profile to olanzapine; whereas, quetiapine was associated with lower risk compared to olanzapine. A case report of low-dose risperidone-induced long QT, confirmed on three independent drug challenges, was described [124] (Table **4**). There are no reported cases of lithium induced TdP.

Antidepressant medications may also prolong the QT interval (Table **3**). Citalopram and escitalopram are reported as drugs with known risk for TdP, and desipramine, imipramine, nortriptiline, clomipramine, trimipramne, mirtazapine, and venlafaxine are listed as drugs with possible increased risk for TdP [125]; (www.crediblemeds.org). Of the cases cited associated with antidepressant use and TdP, at least one additional well established risk factor for QTc prolongation was present in 92.2 % of case reports [126)]. A recent meta-analysis of prospective studies of QT prolongation associated with antidepressant use (not TdP) showed that SSRI and tricyclic antidepressants were associated with a small dose-dependent increase in QTc interval compared to placebo. Citalopram was associated with significantly greater QTc prolongation than sertraline, paroxetine, and fluvoxamine [127]. When citalopram is not prescribed based on risk factors for TdP, use of escitalopram is not likely the safest alternative. Based on current literature, fluoxetine, fluvoxamine, and sertraline appear to have similar, lower risk for QT prolongation, and paroxetine appears to have the lowest risk [128]. Fluoxetine and its metabolite, norfluoxetine, citalopram and escitalopram prolong the QT interval by directly inhibiting the hERG potassium channels and by disrupting channel protein trafficking reducing the number of channels on the cell membrane [129] (Table **3**).

Some anti-cancer drug treatments have been associated with known or possible increased risk of TdP (Table **2**). Arsenic trioxide, administered daily, as a 2-hour infusion of 0.15 mg/kg in patients with relapsed or refractory acute promyelocytic leukemia, prolongs the QT interval increasing risk of TdP [130]. Therefore, patients treated with arsenic trioxide should be monitored for prolonged QT intervals, presence of T-U wave alternants and ventricular arrhythmia [32]. Arsenic trioxide inhibits the trafficking of hERG channels from the endoplasmic reticulum to the cell membrane [131] (Table **3**). Anthracyclines have also been shown to induce TdP and to increase the sensitivity of IKr-blocking drugs to induce TdP; the latter effect is often observed soon after initiation of treatment [132]. Drugs with vascular endothelial growth factor receptor (VEGFR) and tyrosine kinase inhibitory activity (TKI) are known to cause cardiac toxicity [133] (Table **3**). A recent meta-analysis of randomised phase II and III trials compared arms with and without sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. Four times greater risk for QTc prolongation was observed in the patients exposed to VEGFR- TKI than in the control arm. However, only sunitinib and vandetanib were associated with a statistically significant risk of QTc prolongation, with higher doses of vandetanib linked to a greater risk. At least three cases of TdP and nine sudden deaths have already been reported with vandetanib. This drug has been approved for the treatment of metastatic medullary thyroid carcinoma. However, its use is restricted via a Risk Evaluations and Mitigation Strategy program due the associated increased risk of arrhythmia and sudden death [133]. In addition, Vandetanib is metaboliced via cytochrome P450 isoenzyme CYP 3A4; thus, high plasma levels of vandetanib may result during treatment with CYP 3A4 inhibitors. Vandetanib should not be combined with other drugs that prolong the QT interval. Ceritinib has been recently added to the list of drugs with possible risk to TdP and to be avoided in patients with LQTS.

Several other drugs and drug classes have also been reported associated with increased risk of TdP; namely, cisapride, felbamate, tacrolimus, probucol, indapamide, moexipril and tizanidine, arsenic trioxide, probucol, methadone,

alfuzosin, octreotide, dolasetron, ondansetron, and intracoronary papaverine administration [134, 135] (Table **2**). Serotonin agonists of the tryptan class (sumatriptan, naratriptan and zolmitriptan) have also been associated with increased risk for TdP. Ranolazine, an anti-anginal drug, has been shown to induce a modest increase of the QT interval apparently not associated with increased risk of TdP [136]. This effect is achieved by inhibition of hERG channel (Table **3**). The phosphodiesterase III inhibitors, anagrelide and cilostazol, are listed as drugs with known risk of TdP. In experimental animals, cilostazol treatment augmented the incidence of cardiac arrhythmias due to both epinephrine and coronary occlusion. Cilostazol produced large increases in cAMP levels in the myocardium [137]. It has been proposed, that the increases in cAMP, like in beta-receptor activation, may contribute to increased incidence of ventricular arrhythmias and mortality associated with its use. Beta-adrenergic receptor stimulation induced either by increased sympathetic stimulation, or agonists such as albuterol, terbutaline, salmeterol, isoproterenol, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine, increases (upregulates) the number of L-type calcium channels in cardiac fibers, facilitating the development of early afterdepolarizations in the presence of long QT. Therefore, in the presence of an already long QT irrespectively of its etiology, administration of beta-1 receptor agonists may trigger a ventricular arrhythmia.

RISK FACTORS AND PREDICTORS OF DRUG-INDUCED TdP

Presence of congenital long-QT syndrome, bradycardia, age, gender, systolic dysfunction, HIV, hypokalemia hypomagnesemia are well-known risk factors for drug-induced TdP. Coexistence of two or more of these factors in an individual increases the risk of drug-induced TdP. For example, prolonged QT in the elderly has been reported associated with a greater incidence of ventricular arrhythmias [138].

Gender. Females commonly have longer QTc intervals than males, and have a greater propensity to develop TdP than males (17, 138-140). Nearly 66% of the cases of drug-induced TdP occur in women. Clinical and experimental studies show that female gender is associated with a longer corrected QT interval at baseline and a greater response to drugs that prolong the QT interval. Even in the presence of a drug that mildly blocks IKr and seldom or mildly prolongs the QT interval, women are still more prone to drug-induced TdP [5, 139]. Amiodarone, bepridil, quinidine, disopyramide, ibutilide, sotalol, erythromycin, pimozide, probucol, cisapride, terfenadine and halofantrin are among the drugs reported to increase risk of TdP in women [17, 139, 140]. Further, genetic defects of K^+ channels that may be asymptomatic in normal conditions may precipitate drug-induced arrhythmia in women more frequently than in men. It has been proposed that women have a reduced cardiac 'repolarization reserve' possibly due to an effect of estrogens or lack of testosterone. Estrogens are known to facilitate bradycardia-induced prolongation of QT and emergence of arrhythmia; whereas, androgens shorten the QT interval and blunt the QT response to drugs [139]. Patients with male hypogonadism, such as in Klinefelter syndrome, a sex chromosomal aneuploidy [XXY], shortened the QT interval by treatment with testosterone [140-142]. These subjects may be at a higher risk of developing short QT syndrome and may in theory be more resistant to long QT drugs. It proposed that genes on the X chromosome could be involved in regulation of the QTc interval [140-142].

Heart rate. Bradycardia is associated with longer action potential and QT interval, greater transmural dispersion of repolarization, and increased risk of TdP by QT prolonging drugs and some forms of congenital LQTS. As for drugs that inhibit the IKr currents, the arrhythmogenic effect of low serum K^+ is enhanced in the presence of bradycardia [45, 143]. Estrogens potentiate bradycardia-induced QT prolongation [139]. The protective effects of a rapid rhythm on TdP, is well documented. Dofetilide, a Class III antiarrhythmic, induced more QT prolongation after rhythm conversion than during rapid-rate atrial fibrillation. Cardioversion of atrial fibrillation is known to increase the risk of long QT, whereas, persistent atrial fibrillation has a protective effect for drug-induced long QT [5]. Similarly, autonomic block was shown to increase ibutilide-induced QT prolongation [144].

Serum potassium and LQTS. Unlike most K^+ currents, the magnitude of the IKr current is reduced by low extracellular K^+ concentrations, further prolonging repolarization [143]. This probably explains the marked QT prolongation and the induction of TdP observed in patients receiving an IKr antagonist in the presence of low serum K^+ [145]. Hypokalemia increases the incidence of arrhythmias in subjects with LQTS, and in the presence of bradycardia [45, 143]. Maintaining high normal (4.8 mEq/lt) serum potassium levels markedly reduced quinidine-induced QT prolongation and QT variability, and reversed the morphological QT abnormalities, including U waves and bifid T waves [146]. Increases in serum K^+ to levels above 4.0 mEq/lt have also been reported to correct the ECG abnormalities in subjects with LQTS2 [147]. It has been proposed that the conventional lower limit for serum K^+ should be raised in patients with LQTS, either congenital or acquired, as well as for subjects scheduled to receive treatment with drugs known to prolong the QT interval. Drug-induced increases in serum potassium shorten the QT interval and reduce ventricular extrasystoles. In a randomized, double-blind, crossover, placebo controlled trial, in patients with class II-III chronic heart failure, amiloride increased serum potassium by 0.4 mmol/l, reduced premature ventricular contractions, shortened the QT interval by 10 ms, and reduced QT dispersion from 65.7 ms to 50.9 ms [148]. Similarly, in patients with coronary artery disease, spironolactone treatment was associated with a 75% reduction in ventricular extrasystoles and shortening of the QT interval from 440 +/- 28 to 425 +/- 25) [149].

PAST MEDICAL HISTORY/FAMILY HISTORY.

A previous history of drug-induced TdP predicts excessive QT prolongation when exposed to a QT-prolonging drug. The effects of d, l-sotalol (2mg/kg, iv) on the QT interval and development of TdP were studied in a cohort of subjects with a history of TdP in association with QT-prolonging drug use and in age and sex matched controls [75]. Although there were no differences in baseline QTc

intervals between groups, sotalol increased QTc interval duration from 422+/-17 to 450+/-22ms in controls, and from 434+/-20 to 541+/-37ms in subjects with a previous history of drug-induced TdP. Further, TdP occurred in 3/20 (15%) in the study cohort, but in none of the controls [75]. Assuming no differences in sotalol pharmacokinetics among groups, the findings suggest that subjects with a history of drug-induced TdP, despite normal QTc at baseline, have subclinical repolarization defects that were unmasked by sotalol. The findings also indicate that a normal QTc at baseline does not preclude excessive QT prolongation and even development of TdP when exposed to a QT-prolonging drug (low repolarization reserve). Therefore, a previous history of drug-induced TdP, even in the presence of a normal QTc interval duration, should preclude further use of QT prolonging drugs. It is quite possible that subclinical ion channel mutations may account for the increased risk of QT lengthening and TdP observed in these individuals.

When exposed to a QT-prolonging drug, relatives of subjects with a history of long QT, may also be at an increased risk for QT prolongation [150, 151]. The effect of intravenous quinidine was studied in relatives of subjects who developed long QT after administration of QT-prolonging drugs, and in relatives of subjects who failed to prolong the QTc interval (controls). No differences in QTc were observed at baseline or after quinidine between groups. However, quinidine induced a larger increase in the interval from the peak to the end of the T wave in first-degree relatives of patients who prolonged the QT interval than in control relatives. These findings suggest the existence of a genetic predisposition to acquired (drug-induced) LQTS [150, 151]. Further, greater QT interval variability was found in subjects with a history of drug-induced transient QT lengthening >600 ms and/or TdP, than in controls [150]. These findings suggest that repolarization inhomogeneity, assessed through measurements of QT dispersion, may predict drug-induced TdP.

PRACTICAL ASPECTS RELATED TO PATIENT CARE

Progress in the understanding of ion-channels assembly, function and regulation, in the pharmacogenomics of channelopathies, and in the education of health care personnel on risk factors and drug actions, is needed to improve the prevention of drug-induced severe and often fatal arrhythmias. The fact that only few patients receiving drugs reported to prolong the QT interval show QT prolongation and/or develop ventricular arrhythmias, indicates that patient-specific genetics, and/or acquired risk factors, are determinant. The following practical aspects may guide the practitioners in prescribing drugs with known risk of severe arrhythmias and sudden death.

1. Past Medical History. Obtain information about risk factors: congenital or acquired LQTS, history of arrhythmia and/or syncope, seizures, either spontaneous or associated with drug use, presence of ischemic heart disease, cardiomyopathy and/or systolic dysfunction-heart failure, and HIV.
2. Medication history. Determine drug-use associated with previous arrhythmia /syncope / seizure or long QT. If event was associated with drug use, collect information about drug and drugs administered, doses, route of administration, drug-interactions, and concomitant medications. A previous history of drug-induced TdP should preclude the use of a QT prolonging drug, or if need to be used, use under close monitoring. On current medication lists, check for QT-prolonging drugs alone or combined with drug-metabolism inhibitors. Use of two or more drugs known to prolong the QT should be avoided or if required, provide appropriate monitoring; i.e., antidepressants plus fluoroquinolones. Beta-receptor agonists, sympathomimetics, and/or estrogens should be avoided in the presence of long QT or during treatment with QT prolonging drugs.
3. Family history. Family history of congenital or acquired LQTS, history of arrhythmias / syncope/seizures. Relatives of these patients are at a higher risk of developing excessive QT prolongation and TdP when treated with a QT prolonging drug.
4. Risk factors. Identify additional risk factors and combinations of risk factors. Women are at greater risk of TdP than men. Elderly females on antipsychotic or antidepressant medication, needing antiarrhythmic treatment and/or antibiotic treatment must be carefully monitored. Bradycardia as well as hypokalemia increase risk of TdP.
5. Baseline ECG. Examine for heart rate (bradycardia), QTc duration and dispersion, presence of T wave abnormalities, U waves, and T wave alternants. QTc values greater than 450 msec for men and greater than 470 msec for females are usually considered as abnormally prolonged. Estimate QT dispersion using the difference between the maximum and the minimum QTc in any thoracic lead. Values greater than 80 msec are considered abnormally prolonged. If QTc is already prolonged and if dispersion is increased, drugs that further affect the QT interval must be avoided. Such a combination further increases the likelihood of developing drug-induced TdP [97].
6. Serum electrolytes. Obtain serum K^+, magnesium and creatinine levels before starting treatment with a QT-prolonging drug. Normalize serum K^+ and magnesium if low. Assure normal renal function when administering QT prolonging drugs that are mainly eliminated by the kidney. Avoid excessively high levels of QT prolonging drugs.
7. Treatment plan and follow-up plan. Avoid drug combinations known to prolong the QT interval. If a long QT drug must be used, it should be used at low doses if possible, avoiding high peak levels and intravenous administration. Monitor QT on ECG during treatment. Avoid use of two or more drugs known to prolong the duration of the QT interval, and the combined use of long QT drugs with drugs that inhibit their metabolism and may induce accumulation and high plasma levels. Avoid sympathomimetics.

8. Genetic testing. Incorporate genetic testing in high-risk populations (family history, previous multiple syncopal/seizures episodes, previously documented TdP arrhythmia, cardiac arrest/resuscitation).

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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