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REVIEW ARTICLE

Drug-induced life-threatening arrhythmias and sudden cardiac death: A clinical perspective of long QT, short QT and Brugada syndromes

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Abstract Sudden cardiac death is a major public health challenge, which can be caused by genetic or acquired structural or electrophysiological abnormalities. These abnormalities include hereditary channelopathies: long QT, short QT and Brugada syndromes. These syndromes are a notable concern, particularly in young people, due to their high propensity for severe ventricular arrhythmias and sudden cardiac death.

Current evidence suggests the involvement of an increasing number of drugs in acquired forms of long QT and Brugada syndromes. However, drug-induced short QT syndrome is still a rarely reported condition. Therefore, there has been speculation on its clinical significance, since few fatal arrhythmias and sudden cardiac death cases have been described so far.

Drug-induced proarrhythmia is a growing challenge for physicians, regulatory agencies and the pharmaceutical industry. Physicians should weigh the risks of potentially fatal outcomes against the therapeutic benefits, when making decisions about drug prescriptions. Growing concerns about its safety and the need for more accurate predictive models for drug-induced fatal outcomes justify further research in these fields.

The aim of this article is to comprehensively and critically review the recently published evidence with regard to drug-induced life-threatening arrhythmias and sudden cardiac death. This article will take into account the provision of data to physicians that are useful in the identification of the culprit drugs, and thus, contribute to the prompt recognition and management of these serious clinical conditions.

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PALAVRAS-CHAVE
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Torsades de pointes;
Síndrome do QT curto;
Síndrome de Brugada;
Preparações farmacêuticas

Arritmias potencialmente fatais e morte súbita cardíaca induzidas por fármacos: uma perspetiva clínica das síndromes do QT longo, QT curto e Brugada

Resumo A morte súbita cardíaca é um desafio significativo para a saúde pública, pode desencadear-se de anormalidades estruturais ou eletrofisiológicas, tanto genéticas como adquiridas, e abranger as assim chamadas canalopatias hereditárias: síndromes do QT longo, QT curto e Brugada. Essas síndromes são um problema considerável, particularmente para os jovens, pela sua elevada propensão para arritmias ventriculares graves e morte súbita cardíaca.

A evidência atual sugere o envolvimento de um número crescente de fármacos nas formas adquiridas das síndromes do QT longo e Brugada. No entanto, a síndrome do QT curto induzida por fármacos é ainda uma condição raramente reportada. Consequentemente, especulação tem surgido sobre o seu significado clínico, uma vez que poucos casos de arritmias fatais e de morte súbita cardíaca foram descritos até ao momento.

A pró-arritmia induzida por fármacos é um desafio crescente tanto para médicos como para entidades reguladoras e indústria farmacêutica. Os médicos devem pesar o risco de desfechos potencialmente fatais com os benefícios terapêuticos, aquando da tomada de decisões na prescrição de fármacos. As preocupações crescentes sobre a sua segurança e a necessidade de modelos preditivos mais precisos para desfechos fatais induzidos por fármacos justificam pesquisas adicionais nesses domínios.

O objetivo deste artigo foi rever, de forma abrangente e crítica, a evidência publicada recentemente, no que diz respeito às arritmias potencialmente fatais e morte súbita cardíaca induzidas por fármacos, tendo em consideração o fornecimento de dados úteis para médicos na identificação dos fármacos responsáveis e, assim, contribuir para o pronto reconhecimento e gestão desses quadros clínicos graves.

Introduction

Sudden cardiac death

Remarkably, sudden cardiac death (SCD) accounts for about a quarter of the 17 million deaths attributable to cardiovascular diseases every year worldwide.[1]

Coronary artery disease (CAD) is still the leading cause of these deaths, particularly in the elderly. However, primary cardiac arrhythmias and cardiomyopathies are the most common causes of SCD in young people.[2,3] Ventricular fibrillation (VF) is the most common arrhythmia in SCD.[4] In fact, around 50% of SCD cases are due to VF and/or ventricular tachycardia (VT).[3] They predominantly occur out-of-hospital, explaining the low survival rates (i.e., <10%) of patients with VF.[5] Conversely, asystole and pulseless electrical activity (PEA) have been emerging in SCD for indefinite reasons.[3] Interestingly, in patients with reported out-of-hospital sudden cardiac arrest (SCA), antipsychotic drugs have shown to be significant predictors of PEA versus VF/VT.[6]

SCD can be caused by an acquired and/or a genetic background of susceptibility, arising from either electrophysiological (e.g., inherited channelopathies) or structural cardiac abnormalities (e.g., CAD).[1]

Inherited channelopathies

Long QT syndrome (LQTS), Brugada syndrome (BrS) and short QT syndrome (SQTS) are rare inherited arrhythmia disorders arising from ion channel abnormalities, which in turn are termed channelopathies. These syndromes are highly concerning, particularly in young people, due to their high propensity to suffer severe ventricular arrhythmias and sudden cardiac death.[7]

Since the overwhelming majority of patients with inherited channelopathies have no structural heart diseases, an electrocardiogram (ECG) is a valuable tool both in detecting features of these syndromes and in early SCD risk stratification.[1,7]

QT prolongation, torsades de pointes and congenital long QT syndrome

The QT interval represents the electrocardiographic index of ventricular repolarization and depolarization.[8] Because the QT interval varies inversely with heart rate, several correction formulas (e.g., Bazett, Fridericia) allow us to determine a heart rate-corrected QT (QTc) interval. Fridericia's formula provides a more accurate assessment at extremes of heart rate than Bazett's formula and, therefore, it is preferred in such cases.[9,10]

The expert group from the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) gives an upper limit of normal (i.e., estimated 99th percentile) for abnormally prolonged QTc intervals of 470 ms and 480 ms in otherwise healthy post-pubertal males and females, respectively.[11] Patients with an absolute QTc interval of >500 ms are considered to be at risk for

developing torsades de Pointes (TdP), a polymorphic ventricular tachycardia that may shift into VF and lead to SCD.[11,12]

Congenital QT prolongation is due to various genetically based LQTSs. Thirteen congenital types of LQTS have been reported thus far. The KCNQ1 (LQTS 1), KCNH2 (LQTS 2) and SCN5A (LQTS 3) genes encompass approximately 90% of all genotype-positive cases.[1,3] LQTS types 1 and 2 are caused by the loss-of-function mutations of the KCNQ1 and KCNH2 genes encoding the α-subunit of slow (I_{Ks}) and rapid (I_{Kr}) components of the delayed rectifier potassium currents, respectively.[7,13,14] Gain-of-function mutations of the SCN5A gene encoding the α-subunit of the cardiac voltage-gated sodium channels are responsible for LQTS type 3.[15] Genetic testing identifies a disease-causing mutation in about 75% of clinically definite LQTS, which proves its diagnostic significance.[16]

TdP may clinically present as syncope, SCA or SD,[3,13] beginning on average at the age of 12.[7]

The Schwartz risk score is still a widely used diagnostic tool, and is based on clinical presentation, family history and ECG characteristics. The authors currently consider a cut-off value of $\geq$3.5 to be highly accurate in showing a high probability of having LQTS.[17] Additionally, the panel of experts for the latest guidelines from the European Society of Cardiology proposed a QTc $\geq$480 ms in repeated 12-lead ECG as diagnostic criteria, or detection of at least one unequivocally gene culprit mutation, regardless of QT interval duration. A QTc $\geq$460 ms can also be diagnostic in a scenario of unexplained syncope. In all the above-mentioned criteria, other causes for QT prolongation should previously be ruled out.[1]

Short QT syndrome

A rare inheritable channelopathy, called Short QT Syndrome (SQTS), was first clinically described in 2000, in three members of one family who presented with abnormally short QT intervals and tall peaked T-waves in the precordial ECG leads.[18]

Gain-of-function mutations in genes encoding cardiac repolarizing K^+ channels (i.e., KCNH2, KCNQ1 and KCNJ2) and loss-of-function mutations of calcium channel *CACNA1C*, *CACNB2* and *CACNA2D1* genes have been associated with SQTS.[1,7,10] However, the diagnostic yield of genetic testing remains low (i.e., about 20%).[16]

SQTS is diagnosed when QTc interval is $\leq$340 ms or, alternatively, should be considered if QTc interval is $\leq$360 ms along with one or more of the following: (1) survival from a VT/VF episode, in the absence of cardiac disease; (2) a confirmed pathogenic mutation; (3) a family history of SQTS, or (4) a family history of sudden death at the age of <40 years.[1]

Apart from congenital SQTS, other clinical scenarios, such as electrolyte disturbances (e.g., hypercalcemia, hyperkalemia), acidosis, increased heart rate and increased levels of acetylcholine or catecholamine can shorten QT interval.

QT shortening can degenerate into paroxysmal atrial fibrillation (AF) and/or VT and potentially lead to SCD.[18,19]

Brugada syndrome

Brugada syndrome (BrS) is a relatively recent clinical entity, first described in 1992 by a set of distinctive ECG features, especially right bundle branch block and ST-segment elevation in right precordial leads (i.e., V_1 to V_3), in the absence of other concurrent factors (e.g., ischemia, structural heart disease or electrolyte imbalance).[20]

BrS is inherited through an autosomal dominant mode of transmission. Approximately 20 culprit genes have been reported thus far.[21] The pathogenesis of congenital BrS is more commonly due to loss-of-function mutations in the *SCN5A* gene. Currently, over 300 *SCN5A* gene mutations have been described, accounting for the vast majority (i.e., approximately 75%) of genotype-positive cases.[22] Nevertheless, genetic testing identifies such mutations in only about 20-25% of BrS patients.[16] The increase in the transient outward potassium current (I_{to}) and the decrease in the L-type Ca^{2+} current ($I_{Ca,L}$) have also been postulated to contribute to the pathogenesis of BrS.[15,21]

Patients with a BrS ECG pattern are often clinically concealed at the time of diagnosis, which in turn is often incidental.[21] In fact, patients may persist asymptomatically for life, but a subgroup of BrS patients can experience syncope, nocturnal agonal respiration and palpitations associated with high risk of fatal arrhythmias (e.g., VT/VF) and SCD, which generally occur in the third or fourth decades of life, mainly at rest or during sleep.[13,15,21] Although BrS affects both males and women, the condition appears to be 8 to 10 times more common in males.[10]

BrS ECG patterns have been categorized as type 1, 2 or 3 according to detailed characteristics of surface ECGs. A coved ST-segment elevation $\geq$2 mm followed by a negative T wave is representative of a type 1 ECG pattern. Type 2 comprises a saddleback ST-segment elevation of $\geq$0.5 mm (i.e., usually $\geq$2 mm in V_2) in at least 1 right precordial lead (i.e., V_1-V_3), followed by a convex shape. T-wave morphology differs in V_1 and it is characteristically positive in V_2. Type 3 pattern is characterized by either a coved or a saddleback appearance with an ST-segment elevation <1 mm.[23] Nonetheless, only type 1 is recognized as diagnostic. Type 2 and type 3 are not specific to BrS and, therefore, it is currently uncertain whether or not they should be considered BrS patterns. However, physicians should be aware and recognize these patterns as they can be an electrocardiographical presentation of some genuine BrS patients.[21]

The diagnostic criteria of BrS were recently updated in the 2016 expert consensus conference on J-wave syndromes,[23] since the criteria proposed in the 2015 guidelines[1] and in the previous 2013 consensus statement[24] tend to overdiagnose cases of the type 1 ECG pattern. Overdiagnosis is unmasked after intravenous sodium-channel blocker challenge with ajmaline, flecainide, pilsicainide or procainamide. In such patients, BrS diagnosis should require that the patient also present with at least 1 of the following: (1) nocturnal agonal respiration, (2) syncope of probable arrhythmic cause, (3) family history of SCD at less than 45 years old with negative autopsy, (4) documented polymorphic VT or VF, or (5) coved-type ECGs in family members. A spontaneous type 1 ECG pattern in at least 1 right precordial lead (i.e., V_1, V_2 and V_3, placed in the 2nd, 3rd and

4th intercostal spaces, respectively) is an independent BrS diagnostic criterion.[23]

Since other acute (e.g., coronary events, metabolic disorders, electrolyte disturbances) and chronic (e.g., ventricular hypertrophy, autonomic nervous system disorders) conditions can bring about ST-segment elevation patterns, diagnosis of BrS is feasible only after these scenarios are ruled out.[21,23]

Aim

The aim of this article is to comprehensively and critically review the recently published evidence with regard to drug-induced life-threatening arrhythmias and sudden cardiac death. It will take into account the provision of data to physicians that are useful in the identification of the culprit drugs, and thus, contribute to the prompt recognition and management of these serious clinical conditions.

Methods

A comprehensive search was carried out through PubMed to identify human-based studies published in English and/or Portuguese, between January 1, 2011 and January 12, 2017. The following keywords were used in combination, both as Medical Subject Headings (MeSH) terms and text words: ''sudden cardiac death'', ''cardiac arrhythmias'', ''long QT syndrome'', ''torsades de pointes'', ''Brugada syndrome'', ''drug-related side effects and adverse reactions'' and ''pharmaceutical preparations''. Additionally, the text words ''arrhythmias'', ''proarrhythmia'', ''torsade de pointes'', ''short QT syndrome'', ''adverse effects'', ''drugs'' and ''drug-induced'' were combined with the abovementioned search terms. The literature search encompassed relevant studies regarding drug-induced proarrhythmia and SCD, especially those which aimed to address the so-called congenital and acquired arrhythmia syndromes LQTS, SQTS or BrS. A clinical perspective was chosen due to the wide range of data within this field. Case reports were excluded, unless they displayed original evidence or were the only source of a causal relationship. Papers that only aimed to address detailed therapeutic strategies were not considered.

A total of 496 studies were identified. Titles and abstracts were initially screened, and full-text articles were retrieved. The reference list of the identified articles was checked for potentially relevant papers. Two reviewers (i.e., first and last author) independently analyzed each study to minimize bias.

The final review ended up comprising a total of 90 articles. Two additional websites (i.e., www.crediblemeds.org[25]; www.brugadadrugs.org[26]) were included as they provide useful information regarding the aim of this review.

Drug-induced proarrhythmia and SCD

Drug-induced proarrhythmia is the outcome of prior or concomitant use of any drug with life-threatening proarrhythmic effects and SCD risk.[10,27] Growing evidence suggests the implication of an increasing number of drugs in acquired forms of long QT (Table 1), short QT to a lesser extent (Table 2) and Brugada syndrome (Table 3).[10]

Drug-induced LQTS

Acquired LQTS is undoubtedly more common than inherited LQTS.[9] Drugs are undeniably the leading cause of acquired LQTS.[28] Notably, in the last decade, drug-induced TdP was the single most common cause of the withdrawal or restriction of the use of drugs that have already been marketed.[12]

The ACCF/AHA scientific statement recognized a QTc interval of >500 ms, or an increase after drug administration of QTc >60 ms from the pre-drug baseline, as alarming signals that should warrant prompt management and correction.[11] In fact, the majority of drug-induced TdP cases has been reported with QTc intervals of >500 ms.[10]

However, data suggests that the magnitude of QTc prolongation does not directly correlate with the risk of developing TdP. Amiodarone and ranolazine are two paradigmatic cases, which undoubtedly cause QT prolongation, but with few reported cases of TdP. Apparently, these agents attenuate the dispersion of ventricular repolarization, which balance out with the QT prolongation effect.[10] Although not yet proven in congenital forms of LQTS, indirect assessment of transmural dispersion of ventricular repolarization using Tpeak-end interval and the Tpeak-Tend/QT ratio (e.g., significantly increased in cigarette smokers) has been demonstrated to properly predict the risk of potentially life-threatening arrhythmias in drug-induced LQTS.[9,10,29,30] QT dispersion (i.e., difference between the longest and shortest QT interval in the 12 ECG leads), is another potential surrogate marker for ventricular repolarization heterogeneity, which was shown to increase with the use of psychotropic drugs.[31]

Nevertheless, the QT interval is still widely used in clinical practice to assess the risk of TdP and SCD, notwithstanding its poor predictive value.[9,32]

Drug interactions with cardiac ion channels are the main mechanisms involved in potentially life-threatening arrhythmias.[27] Theoretically, almost all drugs associated with QT prolongation and TdP block the rapid delayed rectifier potassium current, I_{Kr}, but not all I_{Kr} inhibitors prolong the QT interval and cause TdP.[12,14] However, the use of these channel blockers in the general population has been associated with high risk of SCD.[33]

Various drugs are metabolized by intestinal or hepatic cytochrome P450 (CYP450) enzymes.[14,27] Methadone (i.e., CYP2C19, notably, the *2 variant that is associated with QTc prolongation,[34] CYP3A4 and to a lesser extent the CYP2D6, CYP2B6 and CYP1A2 enzymes[35]), clarithromycin and erythromycin (CYP3A enzymes),[36] domperidone (CYP3A4)[37] and clozapine (CYP2D6)[38] are examples of such drugs. If those pathways are more prone to be inhibited by the concurrent use of other drugs or their activity is impaired by certain gene polymorphisms, extremely elevated drug serum levels and fatal outcomes are expected to occur.[27]

Recently, the nitric oxide synthase 1 adaptor protein (NOS1AP) genetic variation has been identified as a new genetic marker in modulating QT prolongation and SCD, both in congenital and drug-induced LQTS.[28,39] In fact, along

Table 1 Agents implicated in drug-induced QT prolongation and/or torsades de pointes.

Drug Class	Risk category***	Generic name
Antianginals	Known	Bepridil§ [10,38]
	Conditional	Ranolazine[10]
Antiarrhythmics, class Ia	Known	Disopyramide,[19,38] Procainamide,[19] Quinidine[13,14,19,27]
Antiarrhythmics, class III	Known	Amiodarone,[1,10,14,19,27,38,40,42] ‡ Dofetilide,[14,19,27] Ibutilide[19,27,38]
Antiarrhythmics/Beta blockers	Known	Sotalol[1,10,13,14,19,27,38]
Antibiotics, macrolides	Known	Azithromycin,[36,42,71] Clarithromycin,[1,27,36] Erythromycin[1,27,36,38,40] ‡
Antibiotics, quinolones	Known	Ciprofloxacin,[42] Grepafloxacin,§ [27] Levofloxacin,[42,71] Moxifloxacin,[14] Sparfloxacin§ [27]
Antiemetics	Known	Domperidone,[37,73] Ondansetron[19,42,75]
	Possible	Dolasetron,[19] Granisetron[19]
Antifungals	Known	Fluconazole,[27] Pentamidine[38]
	Conditional	Voriconazole[27]
Antihistamines	Conditional	Diphenhydramine[76]
Antimania	Possible	Lithium[9,38,55,87]
Antimalarials	Known	Halofantrine[38]
	Conditional	Quinine sulfate[38]
Antineoplastics	Known	Arsenic trioxide,[77] Vandetanib[77]
	Possible	Dasatinib,[77] Lapatinib,[77] Nilotinib,[77] Sunitinib,[77] Vemurafenib,[77,78] Vorinostat[77]
Antipsychotics	Known	Haloperidol,[8,9,14,27,38,40,41,48,53–56,63,67] Levomepromazine,[8,45,48,53,55,63] Mesoridazine,§ [38] Pimozide,[55] Thioridazine[8,9,14,38,41,67]
	Possible	Cyamemazine (cyamepromazine),[53,54,63] Flupentixol,[55,56] Perphenazine[45]
Antipsychotics, atypical	Known	Sulpiride[55]
	Possible	Aripiprazole,[56] Clozapine,[38,41,53–55,63] Iloperidone,[14] Paliperidone,[38,55,66] Risperidone,[14,38,41,53–56,63,65] Sertindole,[9,38,63] Tiapride[56]
	Conditional	Amisulpride,[53–56,63] Olanzapine,[14,41,53,54,56,63] Quetiapine,[14,27,38,39,41,53–55,63,64] Ziprasidone[8,9,14,38,41,53–55,63]
Antipsychotics/antiemetics	Known	Chlorpromazine,[8,38,45,53,54,63] Droperidol[19,53,54]
	Possible	Promethazine[45]
GI stimulants	Known	Cisapride,§ [10]
General anesthetics	Known	Sevoflurane[19,72] ‡
Opioid agonists	Known	Levomethadyl acetate,§ [19] Methadone[9,14,19,34,35,55]
Opioid receptor modulator	Possible	Buprenorphine[19]
Psychostimulants	Possible	Atomoxetine[79] †
SNRI antidepressants	Possible	Venlafaxine[38,41,50,55]
SSRI antidepressants	Known	Citalopram,[8,27,41,46–48,55] Escitalopram[8,27,38,41,46,48,55]
	Conditional	Fluoxetine,[41] Sertraline[41]
Tricyclic antidepressants	Possible	Clomipramine,[45,55] Desipramine,[45] Imipramine (melipramine),[41,45,55] Nortriptyline[41,45,55]
	Conditional	Amitriptyline,[45,55] Doxepin[55]
Other therapeutic drugs	Not applicable*	Amoxapine,[45] Atropine,[19] Bromperidol,[53] Bupropion,[50] † Cetirizine,[76] Chlorprothixene,[53,55,63] Clotiapine,[48] Depsipeptide,[77] Desflurane,[19] Desloratadine,[76] Enflurane,[19] Fexofenadine,[76] Fluphenazine,[53,63] Ganciclovir,[56] Glycopyrrolate,[19] Halothane,[19] Hydroquinidine,[38] Isoflurane,[19] Levocetirizine,[56] Loratadine,[76] Mizolastine,[38] Moclobemide,[55] Nitric oxide,[72] ‡ Oxatomide,[56] Oxycodone,[19] Pentobarbital,[10] Pilsicainide,[43] Promazine,[48] Propericiazine,[45] Propoxyphene,§ [19] Prothipendyl,[53] Succinylcholine,[19] Verapamil,[39] Zuclopenthixol[53]
Non-therapeutic drugs	Not applicable*	Alcohol,[82] ** Ginseng,[83] Licorice root compounds (glycyrrhizin, flavones)[84]

Adapted from the website www.crediblemeds.org[25] (accessed January 12, 2017). For an extensive and systematically updated list of all available evidence about the offending drugs and corresponding TdP risk categories, please visit www.crediblemeds.org.

Abbreviations: GI: gastrointestinal; SNRI: serotonin and norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TdP: torsades de pointes.

* Not included in the original drug list of CredibleMeds.

† Only in Overdose.

‡ Concomitant use of QT-prolonging drugs.

§ Removed from market.

** Only in binge drinking (i.e., ≥5 alcoholic beverages in one day, during the previous 12 months).

*** TdP risk categories.

Table 2 Agents implicated in drug-induced QT shortening and/or life-threatening arrhythmias.

Drug class	Generic name
Antiarrhythmics	Digitalis[19]
Antiepileptics	Rufinamide,[10,86] Lamotrigine,[86] * Valproic acid[86] *

* Combined with rufinamide.

with P-glycoprotein, a transmembrane efflux pump (i.e., domperidone is one of its substrates[37]), the NOS1AP gene appears to be implicated in the bioavailability of various QT-prolonging drugs, especially calcium channel inhibitors (e.g., verapamil and diltiazem), since it is involved in the inhibition of L-type Ca^{2+} channels.[14]

Apart from subclinical congenital LQTS, drug-induced TdP depends on a multitude of risk factors, which comprise female gender, advanced age and common clinical conditions, such as bradycardia, hypertension, structural heart diseases (e.g., congestive heart failure, hypertrophic

Table 3 Agents implicated in drug-induced Brugada ECG pattern and/or life-threatening arrhythmias in Brugada syndrome patients.

Drug class	Risk category*	Generic name	Class
Anesthetics/analgesics	To be avoided	Bupivacaine,[10,21,23,87] Procaine,[21,23,87] † Propofol[10,21,23,87] †	IIa
	Preferentially avoided	Ketamine[87] † Tramadol[87] †	IIb
Antianginals	Not to be avoided	Diltiazem,[21] Nicorandil,[21] Nifedipine,[21] Nitroglycerine[21]	III
Antiarrhythmics, class Ia	To be avoided	Ajmaline,[7,10,15,21,23,63,87] Procainamide[7,10,15,21,23,87]	I
	Preferentially avoided	Cibenzoline,[21] Disopyramide[21]	IIb
Antiarrhythmics, class Ic	To be avoided	Flecainide,[7,10,15,21,23,63,87] Pilsicainide[7,10,15,21,23,87]	I
		Propafenone[10,21]	IIa
Antiarrhythmics, class III (also Ia, II and IV effects)	Preferentially avoided	Amiodarone[89]	IIb
Antiarrhythmics, class IV	Preferentially avoided	Verapamil[21]	IIb
Antiemetics	Preferentially avoided	Dimenhydrinate,[21,87] Metoclopramide[87]	IIb
Antiepileptics	To be avoided	Oxcarbazepine[21,87]	IIa
	Preferentially avoided	Carbamazepine,[91] ‡ Lamotrigine,[91] ‡ Phenytoin[91]	IIb
Antihistamines	Preferentially avoided	Diphenhydramine,[87] † Terfenadine/Fexofenadine[87]	IIb
Antipsychotics	To be avoided	Loxapine,[21,87] Trifluoperazine[21,87]	IIa
	Preferentially avoided	Cyamemazine,[21,38,87] † Perphenazine,[21,87] † Thioridazine[87] †	IIb
SSRI antidepressants	Preferentially avoided	Fluoxetine,[21,38,87] † Fluvoxamine,[87] Paroxetine[87]	IIb
Tetracyclic Antidepressants	Preferentially avoided	Maprotiline[21,38,87] †	IIb
Tricyclic Antidepressants	To be avoided	Amytriptiline,[21,87] † Clomipramine,[21,38,87] † Desipramine,[21,87] † Nortriptyline[5,21]	IIa
	Preferentially avoided	Dosulepin,[87] † Doxepin,[87] † Imipramine[87] †	IIb
Other antidepressants	To be avoided	Lithium[10,23,38] ‡ [87]	IIb
Substances	To be avoided	Acetylcholine,[15,21,87] Cocaine[10,15,21] † [23,87]	IIa
		Alcohol,† [15,21,23,87] Cannabis,[21,23] Ergonovine[15,21,23,87]	IIb
	Preferentially avoided	Edrophonium[87]	IIb
Other drugs	Not applicable*	Isosorbide dinitrate,[21] Nicotine[92]	Not applicable*

Adapted from the website www.brugadadrugs.org[26] (accessed January 12, 2017). For an extensive and systematically updated list of all available evidence about the offending drugs, corresponding risk categories and classes of recommendation, please visit www.brugadadrugs.org.

Abbreviations: SSRI: selective serotonin reuptake inhibitors.

* Not included in the original drug list.

† Only in Overdose.

‡ Concomitant drug use.

cardiomyopathy) and electrolyte imbalances (e.g., hypokalemia, hypomagnesemia, hypocalcemia).[11,12,38,40,41]

An up-to-date list of cardiovascular and non-cardiovascular drugs (i.e., mainly psychotropics and antimicrobials[10]) implicated in QT prolongation and/or TdP is currently available at www.crediblemeds.org.[25]

Antiarrhythmic drugs

Antiarrhythmic drugs are among the most harmful regarding their high risk of life-threatening arrhythmias. Vaughan Williams class III drugs (e.g., sotalol, dofetilide, ibutilide) lead to the greatest concern for TdP within antiarrhythmics.[27] Apart from the well-known QTc prolongation effect, amiodarone exhibits a low risk of TdP, when used alone.[9,10,42] Nevertheless, TdP has already been reported with concomitant use (e.g., erythromycin and haloperidol).[40] Therefore, ECG monitoring is required in all intensive care unit (ICU) patients receiving amiodarone, since this subset of patients has a high incidence of concomitant use of other QT-prolonging drugs.[42]

Notably, pilsicainide, a class Ic antiarrhythmic drug, triggered TdP in an elderly patient who ended up dying suddenly, two days after receiving it to convert his paroxysmal AF to sinus rhythm.[43]

Antianginal drugs

In spite of its known QT-prolonging effect, low risk of TdP and SCD have been reported with ranolazine,[10,27] including when it is used to treat non-ST elevation acute coronary syndrome in patients with prolonged baseline QTc intervals.[44]

Antidepressant and antipsychotic drugs

Tricyclic antidepressants are well-known risk factors for QT prolongation and TdP, especially in overdose cases.[27,45]

Overall, selective serotonin-reuptake inhibitors (SSRIs) increase the QTc interval, but citalopram and escitalopram seem to incite a more pronounced QTc prolongation in a dose-dependent fashion.[46–48] Nevertheless, the role of citalopram as a trigger of TdP and SCD remains controversial, as there are no concomitant risk factors for QT prolongation and TdP.[49]

Although bupropion and venlafaxine prolong the QTc interval almost exclusively in overdose scenarios, generally, newer non-SSRIs pose a low risk of such effect at therapeutic doses. Their shorter market life may explain the limited data.[50]

In a cohort study, no considerable differences regarding sudden death and ventricular arrhythmia (SD/VA) risks were detected among 11 antidepressants and paroxetine. High risk of SD/VA was only reported with mirtazapine, but the authors reminded us that such outcome was biased by confounding factors. Therefore, cardiac safety was considered similar among antidepressants.[51]

Given the numerous adverse effects of antipsychotics, drug-induced LQTS is truly one of the most dangerous.[27] Overall, first-generation antipsychotics are considered to be more likely to prolong QT interval and have higher risks of ventricular arrhythmias (VAs) and SCD than second-generation antipsychotics.[8,52]

The Food and Drug Administration Adverse Event Reporting System (FAERS) database has been systematically analyzed to detect signals of torsadogenicity.[53,54] In this regard, detecting new potential signals of torsadogenicity (e.g., with amisulpride, cyamemazine and olanzapine) provided new insights for pharmacovigilance in antipsychotics. This is because it allowed updating the Arizona Center for Education and Research on Therapeutics (AZCERT[25]) drug list.[54] One year later, Fanoe et al. combined pharmacovigilance data from various international databases. Only haloperidol, pimozide, sertindole and ziprasidone were considered to be class B* drugs (i.e., ''a drug with pronounced QT prolongation, documented cases of TdP, or other serious arrhythmias'').[55] Alternatively, the data analysis of three national spontaneous reporting systems (i.e., France, Germany and Italy) demonstrated that in all of the national databases studied, TdP events were reported only with amisulpride, aripiprazole, haloperidol, olanzapine and risperidone.[56]

Therefore, available data on haloperidol have consistently favored its marked QT prolongation effect and high risk for TdP and SCD,[53–57] but such outcomes have been disparate for clozapine (low risk of QTc prolongation[58]; ''very strong signals of torsadogenicity''[53,54]) and olanzapine (''a drug considered to be without any risk of QT prolongation or TdP''[55]; ''potential signal of torsadogenicity''[54]; ''very strong signal of torsadogenicity''[53]). Despite ziprasidone having QT-prolonging and torsadogenic effects,[53–55] studies have failed to prove an increased risk of SD, SCD or non-suicide mortality.[59–61] Aripiprazole has a low risk of TdP and SCD, at least in otherwise healthy patients. However, in patients at risk for TdP, it may represent a safety concern, since few studies have been carried in these vulnerable subsets.[62,63] Cases of QTc prolongation, TdP and SCD have been reported with quetiapine, but only with concomitant risk factors for QT prolongation or TdP.[64] Increased QTc prolongation and higher risk of SCD have been documented with risperidone during nighttime, when compared to olanzapine users.[65] These perilous effects are likely due to the increased serum levels of risperidone's active metabolite paliperidone in a dose-dependent manner and not to risperidone alone.[66] Two retrospective cohort studies also made a comparison with olanzapine, but both risperidone and quetiapine were not implicated in higher risk of SD or VAs. According to the authors, olanzapine was chosen as the referent, since it is not linked to substantive QT prolongation.[57]

Exposure to phenothiazine antipsychotics also carries a risk of QTc prolongation and TdP both in therapeutic and overdose settings, particularly with levomepromazine, chlorpromazine and promethazine.[45]

Despite increasing safety concerns, widespread use of antipsychotics with torsadogenic potential has been reported in some European countries in recent years, mostly with haloperidol and thioridazine.[67]

ECG monitoring is strongly recommended at hospital admission in patients with acute psychosis (i.e., recently treated with antipsychotics), due to the increased risk of QTc prolongation.[68] Conversely, Correll et al. affirmed that, unless other comorbidities are present (e.g., cardiac diseases, obesity, hypokalemia), ECG monitoring could

potentially be restricted in young people treated with antipsychotics, as significantly prolonged QTc interval was not demonstrated in this subset of patients. Nevertheless, the authors reinforced the idea that larger studies are required in this regard.[69]

Antimicrobial drugs

Macrolide antibiotics are one of the most prescribed non-cardiovascular QT-prolonging agents, and exhibit increased risk of fatal ventricular arrhythmias or SCD.[27,36] Azithromycin was once considered to be relatively free of adverse cardiac effects. However, new data has been emerging regarding its cardiac safety.[70,71]

Quinolones are broad-spectrum antimicrobials with known risk of QT prolongation.[27,42] It is noteworthy that in a United States veterans study,[71] levofloxacin was significantly associated with serious arrhythmias and death, throughout the 10-day course of therapy.

QT prolongation and TdP have also been reported with antifungal agents, mainly fluconazole.[27]

Anesthetic drugs

Overall, inhaled anesthetics can prolong the QTc interval or increase dispersion of ventricular repolarization to variable degrees. However, only sevoflurane has been associated with TdP risk, though most likely with concomitant risk factors.[19]

An ICU population-based study revealed that a flurane agent had been administered during anesthesia in the overwhelming majority of postoperative patients with QT interval prolongation. Therefore, the authors emphasized the need for QTc interval monitoring in all postoperative ICU patients.[42]

A case of SCA following documented QTc interval prolongation (i.e., 580-600 ms) was reported in a 30-month-old boy during anesthesia induction with sevoflurane and nitric oxide before undergoing plastic surgery for bilateral cutaneous syndactyly. Timothy Syndrome, LQTS type 8 with typical features, including syndactyly, was established by detecting the p.Gly406Arg mutation in the *CACNA1C* gene encoding Cav1.2 L-type calcium channel.[72]

Anticholinergic drugs (e.g., atropine, glycopyrronium bromide) can prolong the QT interval when simultaneously used with anticholinesterases in healthy patients, but TdP may occur when used alone in LQTS patients.[19]

Antiemetic drugs

Domperidone can prolong the QTc interval and increase the risk of serious VAs and SCD.[37,73] SCD risk seems to be higher in the first two weeks of treatment, in patients older than 60 years and those with doses over 30 mg/day.[74]

Serotonin-receptor antagonists (e.g., dolasetron, granisetron and ondansetron) are also known QT-prolonging drugs, but their clinical significance remains unclear, due to few reported cases of fatal cardiac arrhythmias and SCD.[19,75]

Antihistaminic drugs

Apart from not appearing at the forefront of the most common events, adverse cardiac effects are one of the most serious events for patients using first- or second-generation antihistamines.[76]

The low number of antihistamines on the AZCERT drugs list[25] demonstrates the scarcity of pharmacovigilance data reporting TdP events. An analysis of safety reports from the FAERS database revealed new evidence on torsadogenic activity for loratadine, desloratadine, cetirizine and fexofenadine, in addition to diphenhydramine,[76] which was already on the AZCERT list.[25]

Antineoplastic drugs

High TdP event rates are almost exclusively reported with arsenic trioxide. However, BRAF inhibitor vemurafenib, histone deacetylase inhibitors (e.g., depsipeptide and vorinostat) and tyrosine kinase inhibitors (e.g., dasatinib, nilotinib, lapatinib, sunitinib, vandetinib) are also commonly linked to QTc prolongation to varying degrees.[77,78]

Opioid replacement drug therapy

Although more commonly reported at high doses (>200 mg/day), QT prolongation, TdP and SD can occur even at lower doses of methadone (<100 mg/day). This is predominantly in early periods of treatment and/or during concomitant use of either QT-prolonging agents or those which impair methadone metabolism.[35]

Attention deficit hyperactivity disorder drug therapy

QT prolongation is associated with atomoxetine use in overdose.[79] Nevertheless, there is scarce evidence regarding the involvement of stimulants in fatal arrhythmias and SCD.[79,80]

In a non-randomized cohort study conducted in adults, the risk of VA or SD was significantly associated with methylphenidate use. However, the authors argued that the lack of a dose-response effect did not suggest a causal relationship.[81]

Non-therapeutic drugs

Data collected from a large sample representative of the general US population revealed that binge drinkers displayed substantially prolonged QT intervals, compared to non-binge drinkers or non-drinkers.[82]

TdP was reported in a previously healthy 43-year-old woman who presented with syncope after excessive intake of ginseng for 6 months.[83]

Ozturk S et al. described the case of a 59-year-old woman who developed TdP after two days of drinking 5-6 glasses of licorice root tea for constipation. The authors hypothesized that glycyrrhizin was the culprit compound due to its known effects on both cardiac depolarization and repolarization.[84]

Drug-induced SQTS

Drug-induced SQTS is still a rarely reported condition.[85] Therefore, its clinical significance is still unclear, since few fatal arrhythmias and SCD cases have been described thus far.[86]

Antiepileptic drugs

Rufinamide has been reported as a QT shortening agent. In patients receiving rufinamide, the concomitant use of lamotrigine and valproic acid has been associated with a significant decrease in the QT interval.[86]

Drug-induced BrS

Evidence suggests that a rising number of drugs universally used in daily clinical practice can reveal the typical ECG pattern of BrS and, thus, potentially lead to fatal arrhythmias.[87]

Aside from drugs, other clinical scenarios, including febrile state (e.g., hyperthermia, hypothermia) and electrolyte disturbances (e.g., hyperkalemia, hypokalemia, hypercalcemia, hyponatremia), can trigger a type 1 pattern and modulate the occurrence of potentially life-threatening arrhythmias. Some refer to these modifying factors as ''phenocopies''. However, at least for now, it is not proper to do so, due to the lack of data regarding genetic predisposition.[21,23] These conditions are actually more suitably designated as acquired forms of Brugada ECG pattern or BrS.[23]

Psychotropic and anesthetic drugs are the most common non-cardiovascular agents involved in BrS ECG phenotype.[87] Postema et al. founded the website www.brugadadrugs.org to guarantee the worldwide availability of cardiac safety information regarding drug prescription in BrS patients.[26]

Antiarrhythmic drugs

Type 1 BrS ECG pattern is aggravated by drugs that block the cardiac Na^+ channel. Corroborating this finding, some of them (i.e., ajmaline, flecainide, pilsicainide and procainamide) are currently used for diagnostic purposes to unmask such a typical pattern in concealed BrS patients.[15] Nevertheless, it is noteworthy that flecainide has demonstrated an increased risk of SCD when administered to treat AF.[88]

BrS ECG type 1 and type 3 patterns were reported while amiodarone was prophylactically used for AF, following coronary artery bypass grafting.[89]

Antidepressants and antipsychotic drugs

Some tricyclic and SSRI antidepressants and antipsychotics (e.g., lithium) can induce a BrS ECG phenotype by blocking I_{Na} currents.[38,87]

In a population-based study, nortriptyline, an example of such a drug, was associated with a significant 4.5-fold increase in the risk for SCA.[5]

Although fluvoxamine and paroxetine at therapeutic doses and fluoxetine in overdose can trigger a BrS ECG pattern, no severe VAs have been reported thus far. Similarly, phenothiazine antipsychotics (including cyamemazine, perphenazine and thioridazine) are well-known culprit agents in drug-induced BrS, but without causing fatal VAs.[87]

Epilepsy and antiepileptic drug therapy

Epilepsy is considered to be an independent risk factor for life-threatening arrhythmias and SCD. In fact, epilepsy has been associated with a two- to three-fold higher risk for SCD than in the general population and with a six-fold higher risk in poorly controlled patients.[90]

Recently, Ishizue et al. concluded that the concomitant use of sodium channel-blocking antiepileptic drugs, including carbamazepine, phenytoin and lamotrigine, significantly caused a BrS type 1 pattern. Conversely, the authors admitted the inability to assess the 12-lead ECGs of a large proportion of epilepsy patients, before and after antiepileptic therapy. As a result, epilepsy as a confounding factor cannot be ruled out.[91]

Bardai et al. revealed the increased risk of SCD with the use of sodium channel-blocking antiepileptics in epilepsy patients (i.e., carbamazepine and gabapentin) that was independent from the underlying epileptic condition. In addition, off-label drug use in non-epileptic patients has also been correlated with increased risk for SCD, similarly to epilepsy per se. If we transfer these conclusions to clinical practice, measures involving seizure control with antiepileptic drugs are required, but the risk of SCD must always be taken into account.[90]

Anesthetic drugs

Despite having one of the safest profiles within modern anesthetics, high doses of propofol can lead to SCD, a condition termed ''propofol infusion syndrome''. A Brugada ECG pattern is commonly seen before ''propofol infusion syndrome'' occurs. Thus BrS is, until proven otherwise, an underlying mechanism for potentially life-threatening arrhythmias and SCD.[10,87]

Antiemetic drugs

Metoclopramide has been reported to trigger typical BrS ECG features at therapeutic doses, without being involved in serious arrhythmias.[87]

In a population-based nested case-control study, oral exposure to metoclopramide demonstrated higher risk for developing SCD than oral exposure to domperidone. However, the authors alleged that this was an unexpected outcome and thus recommended further research in this regard.[74]

Antihistaminic drugs

Both first- and second-generation antihistamines (e.g., diphenhydramine almost exclusively in overdose and terfenadine) have been involved in drug-induced BrS.[87]

Non-therapeutic drugs

Type 1 Brugada ECG pattern was documented in a woman with a family history of SCD, who used topical nicotine patches for smoking cessation at high doses.[92]

Cocaine and alcohol are two well-known triggers of BrS-like ECG pattern and VF, both alone or with cocaethylene, the ensuing metabolite of their combined use.[15,87]

Discussion and conclusions

An increasing number of cardiovascular and non-cardiovascular drugs have been broadly associated with proarrhythmia and SCD. In fact, drug-induced proarrhythmia should always be viewed as a prelude to SCD.[10] Hence, it has been a growing challenge for physicians, the regulatory agencies responsible for assessing drug safety and the pharmaceutical industry due to the pressure to create newer and safer agents.[87]

Physicians should weigh the risks of potentially fatal outcomes against therapeutic benefits when making decisions about drug prescriptions. In the event of a suspicious drug-induced proarrhythmia, withdrawal of the offending drugs is recommended, but only after ruling out other concomitant risk factors.[12]

Physicians who are aware of inherited arrhythmia syndrome should provide a letter or a similar useful tool to their patients and family members.[15] Postema et al. provide an example of such a letter, available in various languages on their website, which contains drugs that should be avoided or contraindicated in BrS patients.[26]

The uncertainty regarding the correlation between the magnitude of QT interval prolongation and the risk of TdP events should lead to a search for more knowledge on risk stratification of drug-induced TdP, given the possible devastating consequences.

Post-approval safety studies provide reliable data for physicians about drug safety. Given the tremendous significance in clinical practice, this review highlights the need for synergy among physicians, regulatory agencies and drug manufacturers, and the need for routine spontaneous reporting and drug utilization analyses.

Future studies to obtain further knowledge and a better understanding of genetic variants related to pharmacokinetics and pharmacodynamics are crucial to more accurately predict drug-induced fatal outcomes for at-risk patients and to clarify which drugs can be administrated more safely. This may avoid the inappropriate withdrawal of certain drugs from the market. Undoubtedly, the field of genetics is growing faster than expected, and it will surely play a key role in this major health concern.

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