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AHA SCIENTIFIC STATEMENT

Drug-Induced Arrhythmias

A Scientific Statement From the American Heart Association

ABSTRACT: Many widely used medications may cause or exacerbate a variety of arrhythmias. Numerous antiarrhythmic agents, antimicrobial drugs, psychotropic medications, and methadone, as well as a growing list of drugs from other therapeutic classes (neurological drugs, anticancer agents, and many others), can prolong the QT interval and provoke torsades de pointes. Perhaps less familiar to clinicians is the fact that drugs can also trigger other arrhythmias, including bradyarrhythmias, atrial fibrillation/atrial flutter, atrial tachycardia, atrioventricular nodal reentrant tachycardia, monomorphic ventricular tachycardia, and Brugada syndrome. Some drug-induced arrhythmias (bradyarrhythmias, atrial tachycardia, atrioventricular node reentrant tachycardia) are significant predominantly because of their symptoms; others (monomorphic ventricular tachycardia, Brugada syndrome, torsades de pointes) may result in serious consequences, including sudden cardiac death. Mechanisms of arrhythmias are well known for some medications but, in other instances, remain poorly understood. For some drug-induced arrhythmias, particularly torsades de pointes, risk factors are well defined. Modification of risk factors, when possible, is important for prevention and risk reduction. In patients with nonmodifiable risk factors who require a potentially arrhythmia-inducing drug, enhanced electrocardiographic and other monitoring strategies may be beneficial for early detection and treatment. Management of drug-induced arrhythmias includes discontinuation of the offending medication and following treatment guidelines for the specific arrhythmia. In overdose situations, targeted detoxification strategies may be needed. Awareness of drugs that may cause arrhythmias and knowledge of distinct arrhythmias that may be drug-induced are essential for clinicians. Consideration of the possibility that a patient's arrythmia could be drug-induced is important.

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Many widely used medications may cause or exacerbate a variety of arrhythmias. Numerous antiarrhythmic agents, antimicrobials, and psychotropic drugs and a growing list from other therapeutic classes (neurological agents, anticancer drugs, and many others) can prolong the QT interval and provoke torsades de pointes (TdP). Drugs can also trigger other arrhythmias, including bradyarrhythmias, atrial fibrillation (AF)/atrial flutter (AFL), atrial tachycardia (AT), atrioventricular nodal reentrant tachycardia (AVNRT), monomorphic ventricular tachycardia (VT), and Brugada syndrome. The purpose of this statement is to review drugs that cause or exacerbate arrhythmias, consider risk factors, discuss monitoring strategies, describe methods for prevention and risk reduction, and review treatment options.

METHODS

The following literature search engines were used to identify articles: MEDLINE/PubMed, the Cochrane Library, Embase, and ClinicalTrials.gov. Searches were limited to English language and human subjects (exception: articles with nonhuman subjects describing mechanisms of drug-induced arrhythmias were included). Search terms used to identify articles are presented in Supplemental Table 1. In addition, the reference sections of References 1 and 2 of this article and the reference sections of other identified articles were reviewed to identify additional articles.[1,2] Incidences of drug-induced arrhythmias are listed when available, although the level of evidence varies substantially across reports.

DRUG-INDUCED BRADYARRHYTHMIAS

Bradyarrhythmias are broadly classified as sinus node dysfunction and atrioventricular block. Drugs that inhibit sinus node function can cause sinus bradycardia (heart rate <60 bpm), sinus pauses, or sinus arrest (Supplemental Figure 1). Mechanisms include inhibition of automaticity, slowing of conduction, or prolongation of repolarization in the sinus node. Atrioventricular block occurs when impulse conduction through the atrioventricular node and the His-Purkinje system is inhibited or when refractoriness is prolonged (Supplemental Figure 1).

The overall incidence of drug-induced bradyarrhythmias is unknown, but certain pharmacological classes represent the majority of cases (Table 1).[1,3] Drugs that inhibit sympathetic nervous system activity (β-blockers) or stimulate the parasympathetic nervous system (neostigmine, pyridostigmine) suppress sinus node automaticity. The action potentials of both nodes are dependent on sodium and calcium current, inhibition of which may lead to bradyarrhythmias. Clonidine stimulates central α-receptors and reduces norepinephrine release.[1] Ivabradine inhibits the hyperpolarization-activated cyclic nucleotide-gated funny (I_f) channels in the sinus node (Figure 1).[4] Fingolimod modulates sphingosine 1-phosphate receptors, which regulate heart rate and cardiac conduction (Figure 2).[5]

Drugs that inhibit sinus or atrioventricular node function should be avoided in patients with preexisting dysfunction in the absence of a functioning pacemaker. Combinations of sinus or atrioventricular node inhibitors should be minimized when possible, and maximum daily doses should not be exceeded. Liver and kidney disease can increase plasma concentrations of drugs that rely on these organs for metabolism and elimination. Patients should be educated to recognize and report symptoms of bradycardia.[1]

It is reasonable to monitor patients taking sinus or atrioventricular node–inhibiting drugs with periodic 12-lead ECGs. First-degree atrioventricular block is not an absolute contraindication to receiving these medications, but the PR interval should be monitored to ensure that atrioventricular block is not progressing.

Initial management of a drug-induced bradyarrhythmia includes dose reduction or discontinuation of offending agents unless the medication is necessary and no substitute is available. Notably, although discontinuation can lead to resolution, ≈50% of patients experience persistence or recurrence of bradycardia and may still need a pacemaker, so patient evaluation should continue even after medication discontinuation.[6] Death resulting from drug-induced bradyarrhythmia is uncommon. Rarely, bradycardia-associated TdP can occur in the setting of QT prolongation that is exacerbated by bradycardia. Patients with a compelling indication for a β-blocker or other node-inhibiting drug who experience bradyarrhythmia may require implantation of a permanent pacemaker in order to mitigate long-term risk.[3]

Other precipitating factors (electrolyte abnormalities, infection, hypothyroidism) should be addressed. For short-term management, the parasympatholytic agent atropine 0.5 mg may be administered intravenously every 3 to 5 minutes to a maximum dose of 3 mg. Patients who have undergone heart transplantation without evidence for autonomic reinnervation should not receive atropine because it can cause paradoxical heart block or even sinus arrest.[3] In patients with hemodynamic compromise but low likelihood of coronary ischemia, isoproterenol, dopamine, dobutamine, or epinephrine may be indicated. Temporary transcutaneous or transvenous pacing can be used in refractory cases.[3]

For overdose of sinus or atrioventricular node–blocking agents, gastric lavage or activated charcoal may be useful, depending on timing. Glucagon administered as an intravenous bolus of 3 to 10 mg followed by a continuous infusion of 3 to 5 mg/h is reasonable for patients with symptomatic or hemodynamically unstable bradycardia associated with β-blocker or calcium channel blocker overdose.[3] High-dose regular insulin (1 unit/kg intravenous bolus followed by a continuous infusion of 0.5 units/kg/h) may increase heart rate and

Table 1. Drugs That May Cause/Exacerbate Sinus Bradycardia/Atrioventricular Block

Drug Class	Drug	Incidence, % or Odds Ratio	Mechanism
Acetylcholinesterase inhibitor	Donepezil	0.6–48	Stimulation of activity of the parasympathetic nervous system, leading to inhibition of automaticity of sinus node
	Neostigmine	OR 2.7 (95% CI 1.4–5.4)	
	Physostigmine	…	
	Pyridostigmine	…	
Anesthetic	Bupivacaine	2–32	Reduction in sympathetic activity
	Propofol	14.7	
Antiarrhythmic	Adenosine	1–8	Sinoatrial/atrioventricular node inhibition
	Amiodarone	3–20	Sinoatrial/atrioventricular node inhibition
	Disopyramide	0–4	Sinoatrial/atrioventricular node inhibition
	Dronedarone	0.7–2.3	Sinoatrial/atrioventricular node inhibition
	Flecainide	2–13.2	Atrioventricular node, HPS inhibition; sinoatrial node inhibition in patients with sinus node dysfunction
	Ivabradine	3.7–15.7	Inhibition of I_f channels in the sinus node
	Propafenone	0.7–10	Sinoatrial/atrioventricular node, HPS inhibition
	Quinidine	…	Sinoatrial/atrioventricular node inhibition may be counterbalanced by vagolytic effects
	Sotalol	1.5–17.1	Sinoatrial/atrioventricular node inhibition
Anticancer	Thalidomide	3.2–5.4	…
Antidepressant	Citalopram	0.1–2.4	Na and Ca inhibition
	Escitalopram	…	
	Fluoxetine	…	
Antihypertensive	Clonidine	5–17.5	Stimulation of central α_2-receptors, reducing release of norepinephrine
	β-Blockers (including eye drops)	0.6–25	β-Blockers and non-DHP CCBs: inhibition of automaticity of sinus node
	Diltiazem	4.2–16	
	Verapamil	0–11	
Inotrope	Digoxin	0–7	Increased vagal tone
Sphingosine 1-phosphate receptor modulator	Fingolimod	0.5–3.7	Modulation of the sphingosine 1-phosphate receptors
Vasodilator/antiplatelet	Dipyridamole	0.5–6.7	Increased adenosine leading to direct sinoatrial/atrioventricular node inhibition

Ca indicates calcium; CCB, calcium channel blocker; CI, confidence interval; DHP, dihydropyridine; HPS, His-Purkinje system; I_f, hyperpolarization-activated cyclic nucleotide-gated funny channel; Na, sodium; OR, odds ratio; and …, unknown.

improve hemodynamics in refractory bradyarrhythmias associated with overdose of an atrioventricular node–inhibiting drug.[7] Intravenous dextrose should be coadministered, and electrolytes should be monitored closely. Intravenous calcium chloride or calcium gluconate may be administered to patients with calcium channel blocker overdose.[3] Data demonstrating hemodynamic benefits are variable, but risk is low.

DRUG-INDUCED SUPRAVENTRICULAR ARRHYTHMIAS

Atrial Fibrillation and Atrial Flutter

AF and AFL are characterized by rapid irregular and regular atrial activity, respectively. Distinct P waves are absent in AF; ventricular conduction may be rapid. Atrial activation is more organized in AFL, in which typical forms have a sawtooth pattern. Drugs that may cause or exacerbate AF/AFL (Table 2) include cardiovascular medications, alcohol, stimulants, anticancer agents, and immunomodulators.[1,8–19]

Mechanisms of drug-induced AF vary by medication (Table 2). Many stimulants act via catecholaminergic augmentation, resulting in β-receptor stimulation, shortened atrial effective refractory period, increased cAMP (cyclic adenosine monophosphate), cytosolic calcium, atrial automaticity, and pulmonary vein ectopic depolarizations. Adenosine shortens atrial effective refractory period and promotes pulmonary vein ectopy. Alcohol promotes sympathetic nervous system stimulation, shortens atrial effective refractory period, increases

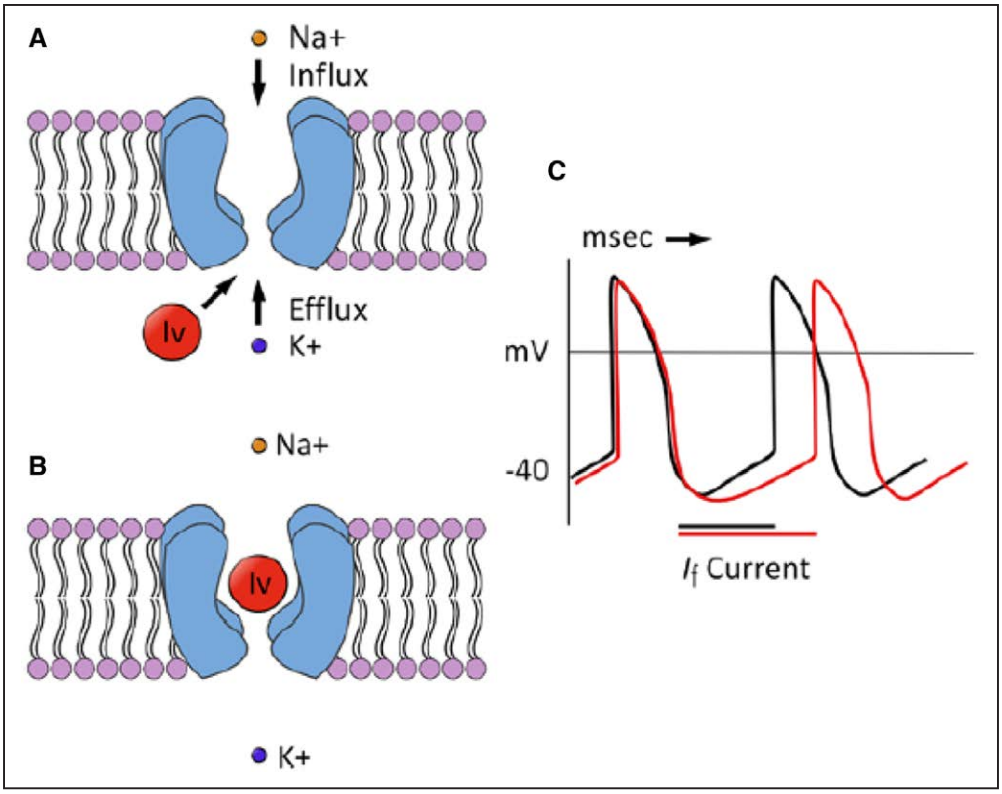

Figure 1. Mechanism of heart rate slowing associated with ivabradine (Iv); inhibition of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels.
Normal HCN channels create the diastolic I_f current (**A**). Ivabradine inhibits ion passage in a current-dependent manner (**B**), which diminishes I_f, slowing diastolic depolarization (red) and heart rate. Reprinted from Psotka and Teerlink.[4] Copyright © 2016, American Heart Association, Inc.

interatrial electromechanical delays, and acts via vagal pathways. The mechanism of bisphosphonates-induced AF is unclear, but these drugs release inflammatory cytokines and shorten atrial action potential duration and effective refractory period. Mechanisms of atrial proarrhythmia for many other agents remain unknown, including for ivabradine, as I_f inhibition has been theorized to exert antiarrhythmic effects. Certain antiarrhythmics can cause or exacerbate AFL, including the sodium channel–blocking drugs flecainide and propafenone, which slow atrial conduction, increase the flutter cycle length, and can result in 1:1 atrioventricular conduction with a wide QRS. Consequently, atrioventricular node–blocking drugs should be prescribed when flecainide or propafenone is used in patients with AFL. Amiodarone may result in AF related to its ability to induce thyrotoxicosis in some patients. Newer mechanisms of drug-induced AF/AFL have been proposed for some drugs such as trastuzumab, which increases inflammation, oxidative stress, and reactive oxygen species, causing

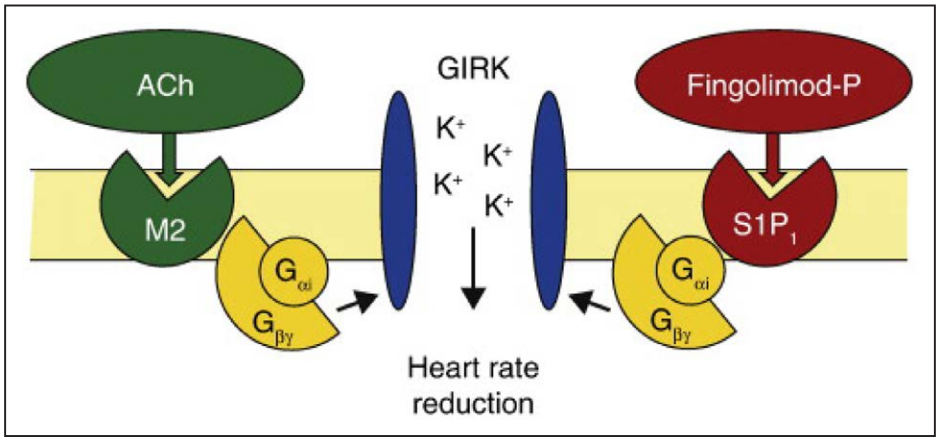

Figure 2. Fingolimod modulation of sphingosine 1-phosphate (S1P1) receptors, leading to heart rate reduction.
Ach indicates acetylcholine; G, G proteins; GIRK, G protein–gated inwardly rectifying potassium; and M2, muscarinic-2. Reprinted from Camm et al.[5] Copyright © 2014, The Authors. Published by Elsevier Inc. This is an open access article under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Table 2. Drugs That May Cause/Exacerbate AF or AFL

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
Antiarrhythmic[1]	Adenosine	1–12	↑ Pulmonary vein ectopic activity
			↓ Atrial effective refractory period/wavelength
	Amiodarone	…	Thyrotoxicosis
	Flecainide	…	Sodium channel blockade, slowing atrial conduction
	Propafenone	Up to 9.0†	Sodium channel blockade, slowing atrial conduction
Anticancer[8]	Tyrosine kinase inhibitors (cetuximab, sunitinib, sorafenib,*[9] ibrutinib[10])	3.3–6.5	↓ nitric oxide signaling, ↑ endothelin-1, lipid accumulation, reactive oxygen species production, inhibition of AMPK, inhibition of K^+ channels, mitochondrial disorders, apoptosis, thyrotoxicosis (sunitinib, sorafenib), ↑ hypertension and ↓ cardioprotective effect through cardiac ↓ PI3K-Akt signaling pathway (ibrutinib)
	Anthracyclines (doxorubicin, aclacinomycin A, 7-con-O-methylnogaril, mitoxantrone)	1.4–13.8	Connexin channels, CaMKII, Ca_2^+ ATPase, reactive oxygen species, mitochondrial dysfunction, apoptosis
	Alkylating agents (cisplatin, melphalan, cyclophosphamide,*[11] ifosfamide)	Up to–15.5	↓ DNA and RNA synthesis, mitochondrial, contractile, endothelial reticulum stress, apoptosis, reactive oxygen species, inflammation, ion channel effects, ATP, lysosome injury, cytotoxic effects
	HER2/Neu receptor blockers (etaracizumab, trastuzumab)	1.2–19.9	Oxidative stress/reactive oxygen species, ↑ inflammation causing ion channel dysfunction and remodeling, apoptosis, ErbB2-ErbB4 signaling
	Antimetabolites (5-fluorouracil, leucovorin)	2.6	Impaired DNA synthesis, coronary spasm, myocardial ischemia
	Microtubule agents (paclitaxel, docetaxel, gemcitabine,[12] gemcitabine+vinorelbine)	1.0–9.4	Cell division, coronary flow, LV systolic pressure effects, possibly sinoatrial node dysfunction (gemcitabine)
	Histone deacetylase inhibitors (belinostat)	4.6	…
Antidepressant (SSRI)	Fluoxetine*	…	…
Antiemetic	Ondansetron*	…	…
Anti-inflammatory	Diclofenac[13]	IR (95% CI): 1.2 (1.1–1.4) vs no NSAID, 1.4 (1.2–1.6) vs paracetamol, 1.1 (1.0–1.3) vs ibuprofen,1.3 (1.0–1.7) vs naproxen	↓ Endogenous antiarrhythmic effect of prostacyclin through ↑ COX-2 inhibition
	COX-2 inhibitors (etoricoxib[14])	HR 1.16 (95% CI, 1.05–1.29)	↓ Endogenous antiarrhythmic effect of prostacyclin through ↑ COX-2 inhibition
		Etoricoxib HR 1.35 (95% CI, 1.19–1.54)	
	Corticosteroids (methylprednisolone)	1.8	Inconsistent associations of AF in patients on corticosteroids; may be secondary to underlying conditions
Antiplatelet	Ticagrelor*	…	Speculated to increase adenosine
Antipsychotic[1,15]	Chlorpromazine	OR, 1.96 (95% CI, 1.44–2.67)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Clozapine	OR, 2.81 (95% CI, 1.24–6.39)	Serotonin receptor subunit 5-HT2A antagonist
			Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Prochlorperazine	OR, 1.22 (95% CI, 1.15–1.29)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities

(*Continued*)

Table 2. Continued

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
	Olanzapine	OR, 1.81 (95% CI, 1.14–2.88)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Risperidone	OR, 1.25 (95% CI, 1.00–1.55)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Quetiapine	OR, 1.55 (95% CI, 1.25–1.92)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Loxapine*	…	Dopamine antagonist, serotonin 5-HT2 blocker
Bisphosphonates	Alendronate	0.5	Equivocal or conflicting data
		OR, 1.86 (95% CI, 1.09–3.15)	↓ Atrial effective refractory period/wavelength
		OR, 1.97 (95% CI, 1.59–2.43)	↑ Release of inflammatory cytokines
		IR, 1.58 (95% CI, 1.07–2.33)	
	Zoledronic acid	0.8–2.2	Equivocal or conflicting data
			↓ Atrial effective refractory period/wavelength
			↑ Release of inflammatory cytokines
Bronchodilator	Albuterol	…	β_2-Adrenergic agonist
	Terbutaline*	…	β-Adrenergic agonist
	Metaproterenol	2.5	β_2-Adrenergic agonist
	Theophylline	…	Phosphodiesterase inhibition
			↑ Atrial automaticity
	Aminophylline	…	Phosphodiesterase inhibition
	Ipratropium bromide	…	Anticholinergic
	Tiotropium	1.7/100 person-y	Anticholinergic
Cannabinoid	Cannabis, synthetic cannabinoids*	…	Adrenergic stimulation, altered atrial coronary or microvascular flow, coronary spasm, postulated ↑ pulmonary vein ectopy, increased sympathetic and parasympathetic activity
Catecholaminergic	Dobutamine	0–18	β-adrenergic agonist
	Dopamine	…	α- and β-adrenergic, dopamine receptor agonist
	Epinephrine	..	β-Adrenergic agonist
Central nervous system depressant	Alcohol	Pooled OR/RR, 1.51 (95% CI, 1.3–17.4)	↓ Atrial effective refractory period/wavelength
			↑ Sympathetic nervous system activity
			↑ Interatrial electromechanical delays
		HR, 1.14 (95% CI ,1.04–1.26)	↑ Vagal activity
		HR, 1.29 (95% CI, 1.02–1.62)	
		HR, 1.60 (95% CI, 1.02–2.51)	
Cognitive function enhancer	Physostigmine*	…	Acetylcholinesterase inhibitor
I_f current inhibitor	Ivabradine	1.3	…
		OR, 1.35 (95% CI, 1.19–1.53)	
		RR, 1.15 (95% CI, 1.07–1.24)	
		RR, 1.24 (95% CI, 1.08–1.42)	
Illicit	Cocaine*[16]	…	Catecholamine excess; increased sympathetic tone; ischemia; hyperthermia; sodium and potassium channel blockade
	Amphetamine, methamphetamine, and derivatives, 3,4-methylenedioxymethylamphetamine* (MDMA, ecstasy)	…	Catecholamine excess from release of norepinephrine, dopamine, and serotonin from central and autonomic nerve terminals

(*Continued*)

Table 2. Continued

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
Immune-modulating agents	Fingolimod	0.5	…
Immunotherapy	Interleukin-2	3.5–6.0	Proinflammatory cytokines, calcium and calcium channel effects, inflammation, activation of c-Src kinases
Inotropes/vasodilators	Levosimendan	0–9.1	↑ Calcium sensitivity
	Milrinone	2.9–5.0	Phosphodiesterase inhibitor
	Enoximone	8.3	Phosphodiesterase inhibitor
Opioid	Morphine	HR, 4.37 (95% CI, 3.56–5.36)	↑ intracellular calcium, activates protein kinase C, open mitochondrial KATP channels
Phosphodiesterase inhibitor	Sildenafil*	…	Selective inhibitor of cGMP-specific phosphodiesterase type 5
	Vardenafil*	…	Selective inhibitor of cGMP-specific phosphodiesterase type 5
Stimulant	Caffeine	…	Phosphodiesterase inhibitor
	1,3 Dimethylamylamine*	…	Indirect sympathomimetic agent
Sympathomimetic agent	Isoproterenol	…	β-Adrenergic agonist
Uterine stimulant	Ergometrine*[17]	…	Ergot alkaloid, coronary spasm, vascular smooth muscle contraction, alteration of autonomic tone

AF indicates atrial fibrillation; AFL, atrial flutter; AMPK, AMP kinase; CaMKII, calmodulin kinase-II; COX, cyclooxygenase; HER2, human epidermal growth factor receptor-2; HR, hazard ratio; HT, hydroxytryptamine; I_f, hyperpolarization-activated cyclic nucleotide-gated funny channel; IR, incidence ratio; LV, left ventricular; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PI3K, phosphoinositide-3-kinase; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; and …, unknown.

*Evidence from case reports only.

†Up to 9% of patients with AF may develop new AFL during propafenone therapy.

ion channel dysfunction and remodeling (Table 2).[18] Proposed mechanisms for AF induced by anticancer drugs are presented in Supplemental Figure 2.[19]

Risk factors for drug-induced AF/AFL are drug specific: adenosine (premature atrial complexes), alcohol (dose >30 g/d, ≥1–3 drinks per day; withdrawal syndrome), and dobutamine (advanced age, prior AF, heart failure).[1] Strategies for prevention include administering the lowest effective dose of AF/AFL–inducing drugs,[1] minimizing or avoiding the use of stimulants, and avoiding excessive alcohol intake (eg, <30 g/d, <7–14 drinks per week, or even abstinence).[1] Patients taking drugs with the potential to provoke AF/AFL should be aware of symptoms; monitor their pulse, heart rate, or rhythm daily, potentially with a wearable monitor if at high risk; and seek medical attention if they have persistent tachycardia, especially with symptoms.

Management of drug-induced AF/AFL includes discontinuation of the offending agent.[1] Many hemodynamically stable patients convert to sinus rhythm spontaneously. Rate control can be achieved with atrioventricular node–blocking agents (β-blockers, CCBs, digoxin). If AF/AFL duration is >48 hours or unknown, the presence/absence of an atrial thrombus should be investigated via transesophageal echocardiography, or ≥3 weeks of therapeutic anticoagulation must be achieved before cardioversion. Hemodynamically unstable patients may require urgent cardioversion, performed as per current guidelines.[20] Longer-term management may include anticoagulation, other pharmacological therapies, or catheter ablation, as recommended.[21] If AF is caused by theophylline or other oral drug overdose, activated charcoal can be considered.

Atrial Tachycardia

AT is characterized by discrete P waves with rates of 100 to 250 bpm. AT may be focal, arising from a single atrial site characterized by uniform P-wave morphology, or multifocal, arising from multiple atrial sites characterized by ≥3 different P-wave morphologies. Common extranodal sites of origin include the crista terminalis, paranodal, paraseptal, periannular, free wall, appendage, pulmonary vein, coronary cusp, or coronary sinus regions.[20] Mechanisms include increased automaticity, triggered activity, or microreentry. Multifocal AT occurs most often in patients with underlying pulmonary or structural heart disease, theophylline use, or hypomagnesemia.

Drugs that can cause AT (Table 3) include catecholaminergic stimulants such as β-agonists or phosphodiesterase inhibitors. Serum theophylline concentrations >20 μg/mL are associated with a higher risk of AT, including multifocal AT.[22] Digoxin toxicity can cause paroxysmal AT with atrioventricular block (Supplemental Figure 3) as a result of (1) inhibition of the Na^+-K^+-ATPase pump, leading to increased intracellular Na^+, increased Na^+-Ca^+ exchange, intracellular calcium overload, and

Table 3. Drugs That May Cause/Exacerbate AT

Drug Class	Drug	Incidence, %	Mechanism
Bronchodilators	Aminophylline	…	Phosphodiesterase inhibitor
	Albuterol	…	β-Adrenergic agonist
	Terbutaline	…	β-Adrenergic agonist
	Theophylline	0–16	Phosphodiesterase inhibitor
Cannabinoid	Cannabis, synthetic cannabinoids	…	Increased sympathetic activity; vasodilatation and reflex tachycardia
Catecholamines	Epinephrine	…	β-Adrenergic agonist
	Isoproterenol	…	β-Adrenergic agonist
Decongestant	Phenylpropanolamine	…	α- and β-adrenergic agonist
Stimulants	Caffeine	…	Phosphodiesterase inhibitor
	Cocaine	…	Catecholamine excess; increased sympathetic tone; ischemia; hyperthermia; sodium and potassium channel blockade
	Amphetamine, methamphetamine, and derivatives	…	Catecholamine excess
Inotropes/vasodilators	Digoxin	0–4	Na^+-K^+-ATPase pump inhibitor
	Dobutamine	…	α- and β-adrenergic agonist
	Milrinone	…	Phosphodiesterase inhibitor

AT indicates atrial tachycardia; ATPase, adenosine triphophatase; and …, unknown.

enhanced atrial automaticity, and (2) vagomimetic or sympatholytic activity, resulting in atrioventricular block. Risk factors for digoxin-induced AT include serum digoxin concentrations >2 ng/mL, kidney disease (elimination is primarily renal), hypomagnesemia, and drug interactions (eg, amiodarone, verapamil, quinidine) leading to elevated serum digoxin concentrations.[1]

Strategies for prevention or risk reduction of drug-induced AT include avoidance of excessive stimulant use; monitoring of serum digoxin concentrations, particularly with chronic or worsening kidney disease or interacting medications; and avoidance of serum theophylline concentrations >20 μg/mL.

Treatment of drug-induced focal AT may include administration of rate-controlling medications and antiarrhythmic drugs (eg, flecainide, propafenone, sotalol, amiodarone, ibutilide), overdrive pacing, catheter ablation, or synchronized direct current cardioversion if hemodynamically unstable.[20] Cardioversion is unlikely to be effective if the arrhythmia mechanism is enhanced automaticity. Some ATs may be terminated or suppressed by adenosine. Treatment of multifocal AT should also include treatment of underlying conditions and magnesium supplementation.[20] Management of digoxin toxicity may require digoxin immune antibody fragments.

Atrioventricular Nodal Reentrant Tachycardia

AVNRT is the most common of the traditional paroxysmal supraventricular tachycardias and is characterized by a regular, narrow QRS tachycardia, often with no visible P waves or a P wave that appears to be part of the QRS complex (pseudo-R prime in lead V_1).[20] The overall prevalence of supraventricular tachycardia is 2.29 per 1000 individuals,[20] of which ≈60% is AVNRT. The proportion of cases that are drug induced is unknown.

Drugs that have been reported to trigger AVNRT are listed in Table 4. Some of these such as theophylline are no longer used widely, whereas others such as caffeine continue to be commonly used. An ECG from a patient with supraventricular tachycardia associated with fluoxetine is presented in Supplemental Figure 4.

AVNRT occurs as a result of a reentrant circuit within 2 pathways of the atrioventricular node; therefore, individuals must have the anatomic substrate of dual atrioventricular nodal pathways. In the majority of cases, anterograde conduction occurs over the slow atrioventricular node pathway, followed by retrograde conduction via the fast pathway.[23] Because atrioventricular nodal conduction velocity is responsive to sympathetic tone and adrenergic stimulation in susceptible individuals, drugs that enhance atrioventricular nodal conduction may trigger AVNRT. In addition, drugs that produce premature extrastimuli may trigger AVNRT by dissociating the refractory periods of the fast and slow pathways, usually inhibiting the fast pathway, allowing slow pathway conduction and initiation of reentry. For drugs that cause AVNRT, both mechanisms are likely present; conduction velocity of the atrioventricular node is enhanced, and drug-induced premature extrastimuli act as the triggers.

Initial management of drug-induced AVNRT is discontinuation of the offending agent. If that is not possible, then limiting the dose/frequency of the inducing drug and monitoring serum drug concentrations, if applicable, are recommended.

Table 4. Drugs That May Cause/Exacerbate AVNRT

Drug Class	Drug	Incidence, %	Mechanism
Amphetamine	Phenylpropanolamine	…	Sympathomimetic
Antipsychotic	Clozapine	…	Vagolytic effects
	Fluoxetine	…	…
Bronchodilators	Albuterol (nebulized)	0–21	β_2-Adrenergic agonist (sympathomimetic)
	Theophylline	…	Adenosine receptor antagonist; phosphodiesterase inhibitor
Catecholamines	Dobutamine	0–12	β_1-Adrenergic agonist (sympathomimetic)
Corticosteroid	Methylprednisolone	…	Rare, unclear mechanism, possibly intracellular electrolytes shift, repolarization abnormalities
Loop diuretic	Furosemide	…	Observed only in children; rapid fluid shift
Stimulant	Caffeine	…	Adenosine receptor antagonist; phosphodiesterase inhibitor
	Methylphenidate	…	Indirect sympathomimetic

AVNRT indicates atrioventricular node reentrant tachycardia; and …, unknown.

For immediate treatment, vagal maneuvers and intravenous adenosine should be the initial strategies.[20] If unsuccessful, intravenous diltiazem, verapamil, or β-blockers are options.[20] Catheter ablation of the slow atrioventricular node pathway has high long-term success rates with a low risk of complications.

DRUG-INDUCED VENTRICULAR ARRHYTHMIAS

Monomorphic Ventricular Tachycardia

VT is a wide QRS complex (≥120 milliseconds) rhythm at rates of ≥100 bpm that is usually regular. Sustained VT lasts ≥30 seconds or causes hemodynamic collapse.[24] Monomorphic VT has a uniform and stable QRS morphology. It can be idiopathic but occurs frequently in patients with underlying structural heart disease such as coronary artery disease, cardiomyopathy (infiltrative, dilated and hypertrophic), sarcoidosis, left ventricular noncompaction, congenital heart disease, and arrhythmogenic right ventricular cardiomyopathy.[24] Depending on hemodynamic response, symptoms may range from mild palpitations to sudden cardiac arrest. VT is an unstable rhythm with high risk for deterioration into ventricular fibrillation and hemodynamic collapse.

Monomorphic VT can occasionally be precipitated by medications (Table 5 and Figure 3). Mechanisms include myocardial sodium channel activation or inhibition, intracellular calcium overload, stimulation of myocardial β_2-receptors, and induction of coronary ischemia. Sodium channel inhibition reduces ventricular conduction velocity and refractoriness, which may promote reentry.[25] This mechanism becomes more important in the presence of fibrosis (scar) such as in the setting of prior myocardial infarction or cardiomyopathy. Potent sodium channel inhibition by Vaughan Williams class IC antiarrhythmic agents (eg, flecainide, propafenone) can lead to an increased incidence of mortality resulting from VT in these patients.[26] In contrast, activation of myocardial sodium channels results in a delay of ventricular repolarization and increases ventricular automaticity.[27] Intracellular calcium overload occurs in patients with digoxin (inhibition of the Na^+-K^+-ATPase pump)[28] and theophylline (phosphodiesterase inhibition) toxicity, resulting in afterdepolarizations and ventricular ectopy (triggered activity), causing VT.[29] Other mechanisms of drug-induced monomorphic VT include coronary steal associated with adenosine and dipyridamole, which can induce myocardial ischemia; stimulation of myocardial β_2-receptors, resulting in ventricular ectopic activity (dobutamine, epinephrine); and arrhythmias secondary to drug-induced coronary vasospasm, myocarditis or cardiomyopathy.

Prevention of drug-induced VT can be achieved by avoidance of the offending agents, careful patient selection, and dose adjustment. Class IC antiarrhythmic agents should not be used in patients with prior myocardial infarction or cardiomyopathy.[26] Therapeutic monitoring of drugs with a narrow therapeutic window (eg, digoxin, theophylline) should be performed, particularly in patients with impaired kidney function (digoxin), hypomagnesemia, or hypokalemia. Serum digoxin concentrations should be maintained at <2 ng/mL,[28] and serum theophylline concentrations should be maintained at <20 μg/mL.[29]

Treatment of drug-induced monomorphic VT depends on the hemodynamic stability of the patient. Hemodynamically unstable patients should be urgently managed with synchronized cardioversion.[24] Stable patients can be treated with intravenous amiodarone, lidocaine, or procainamide and with synchronized cardioversion if necessary after appropriate sedation. For patients with flecainide-induced incessant VT, both intravenous lidocaine and amiodarone have been used successfully.[30,31] Lipid emulsion can also be used in those with VT induced by bupivacaine and local anesthetics.[32]

Table 5. Drugs That May Cause/Exacerbate Monomorphic VT

Drug Class	Drug	Incidence, %	Mechanism
Anesthetic	Bupivacaine	…	Inhibition of sodium channel conductance
	Ropivacaine	…	Inhibition of sodium channel conductance
Antiarrhythmic	Adenosine	Up to 5	Enhanced activity of the sympathetic nervous system via increased arterial chemoreceptor and baroreceptor activity; may also provoke myocardial ischemia resulting from coronary steal
	Amiodarone	…	Inhibition of sodium channel conductance
	Disopyramide	…	Inhibition of sodium channel conductance
	Flecainide	0–13	Inhibition of sodium channel conductance
	Ibutilide	0–9.8	…
	Niferidil	3.7	…
	Procainamide	…	Inhibition of sodium channel conductance
	Propafenone	0–10	Inhibition of sodium channel conductance
	Sotalol	…	…
Anticancer	5-Fluorouracil	…	Coronary vasospasm
	Arsenic trioxide	…	…
	Anthracyclines	…	Myocyte necrosis
	Nivolumab	…	Myocarditis
	Trastuzumab	…	… (Precipitates heart failure)
Anticonvulsant	Lacosamide	…	…
Antidepressant	Bupropion	…	…
	Citalopram	…	…
	Desipramine	…	Inhibition of sodium channel conductance
	Imipramine	…	Inhibition of sodium channel conductance
	Trazadone	…	…
	Venlafaxine	…	…
Antimanic	Lithium	…	Inhibition of sodium channel conductance
Antiplatelet	Dipyridamole	0.03–0.8	…
Antipsychotic	Chlorpromazine	…	Inhibition of sodium channel conductance
	Thioridazine	…	…
β_2-agonist	Terbutaline	0–15	Stimulation of β_2-receptors, leading to ventricular ectopic activity
Ergot derivative	Ergonovine	…	Vasospasm
Herbal	Aconite alkaloids	…	Activation of myocardial sodium channels, increasing permeability to sodium and increasing ventricular automaticity
	Ginkgo biloba	…	…
Illicit	Cocaine	…	Sympathetic stimulation
Inotrope	Digoxin	Up to 7	Inhibition of the sodium-potassium-ATP pump, leading to increased intracellular calcium concentrations, resulting in afterdepolarizations and ventricular ectopic activity
	Dobutamine	0–15.7	Stimulation of β_2-receptors, leading to ventricular ectopic activity
	Milrinone	0–9.5	Phosphodiesterase inhibition
Phosphodiesterase inhibitor	Theophylline	…	Phosphodiesterase inhibition, leading to elevated concentrations of cAMP, causing increased intracellular calcium concentrations, resulting in afterdepolarizations and ventricular ectopic activity
Sympathomimetic	Methamphetamine	…	Sympathetic stimulation
	Ephedrine	…	Sympathetic stimulation
Vasodilator	Levosimendan	…	Calcium sensitization, phosphodiesterase inhibition

cAMP indicates cyclic adenosine monophosphate; VT, ventricular tachycardia; and …, unknown.

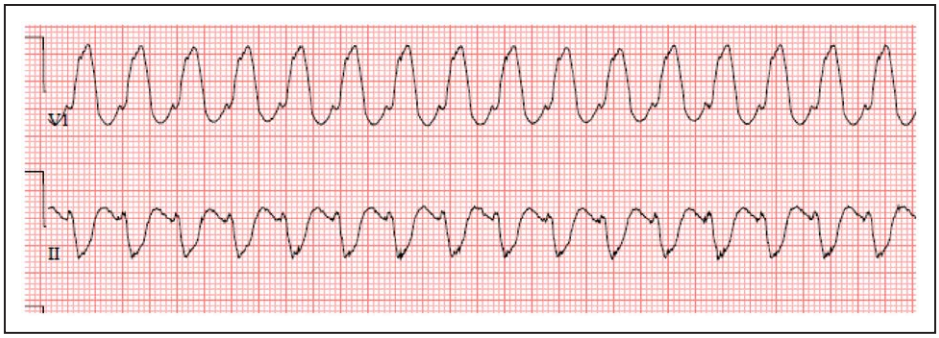

Figure 3. Ventricular tachycardia associated with flecainide.

Brugada Syndrome

Brugada syndrome is an inherited autosomal dominant channelopathy resulting in characteristic electrocardiographic changes (Supplemental Figure 5) and risk for ventricular arrhythmias.[33] Only the type 1 ECG pattern is diagnostic for Brugada syndrome. Drug-induced Brugada syndrome is defined as the presence of normal pretreatment ECG with development of Brugada pattern after exposure to certain drugs, although the genetic substrate may be present.

Most common genetic mutations in Brugada syndrome involve loss of function of myocyte sodium channels (*SCN5A* mutation). Other mutations involve the *SCN10A*, *CACNA1C*, *CACNB2B*, and *KCNJ8* genes.[33] Drug-induced Brugada syndrome can be unmasked by drugs that affect ventricular sodium (most common), potassium, or calcium currents (Table 6 and Figure 4). A detailed list of drugs to be avoided in patients with Brugada syndrome is available online.[34] Many patients with drug-induced Brugada syndrome also have spontaneous Brugada pattern on continuous ambulatory rhythm monitoring.[35]

Brugada syndrome–associated electrocardiographic abnormalities are attributable to transmural dispersion of repolarization, particularly in the right ventricular outflow tract, as well as reduced right ventricular outflow tract epicardial conduction velocity. This may lead

Table 6. Common Drugs Associated With the Brugada Syndrome

Drug Class	Drugs	Incidence of Drug- Induced Brugada Syndrome, %	Incidence of Ventricular Arrhythmias, %	Mechanism of Action
Antiarrhythmic drugs	Ajmaline	39–48.2*	0.15–1.8 (adults)* 10 (children)*	I_{Na} blockade
	Pilsicainide	…	11–18*	
	Flecainide	…	…	
	Procainamide	…	…	
	Propafenone	…	…	
Tricyclic antidepressants	Amitriptyline	2.3–15.3†	0	I_{Na} blockade
	Desipramine			
	Imipramine			
	Nortriptyline			
Anesthetics/analgesics	Bupivacaine	…	…	I_{Na} blockade
	Procaine		…	
	Propofol		…	
Miscellaneous	Alcohol	…	…	$I_{Ca,L}$ blockade
	Cocaine	…	…	I_{Na} blockade
	Lithium	…	…	I_{Na} blockade
	Loxapine	…	…	I_{Na} blockade
	Oxcarbazepine	…	…	I_{Na} blockade
	Trifluoperazine	…	…	I_{Na} blockade

$I_{Ca,L}$ indicates L-type calcium channel; I_{Na}, sodium channel; and …, unknown.

*Patients with suspicion for Brugada syndrome underwent class IC antiarrhythmic challenge, primarily with ajmaline or pilsicainide, and hence represent a population with a high pretest probability. The real-world incidence of drug-induced Brugada syndrome in patients taking class I antiarrhythmic agents is not known.

†Data on the incidence of tricyclic antidepressant–induced Brugada syndrome are available only in patients with overdose. The real-world incidence of drug-induced Brugada syndrome in patients on therapeutic doses of these agents is not known.

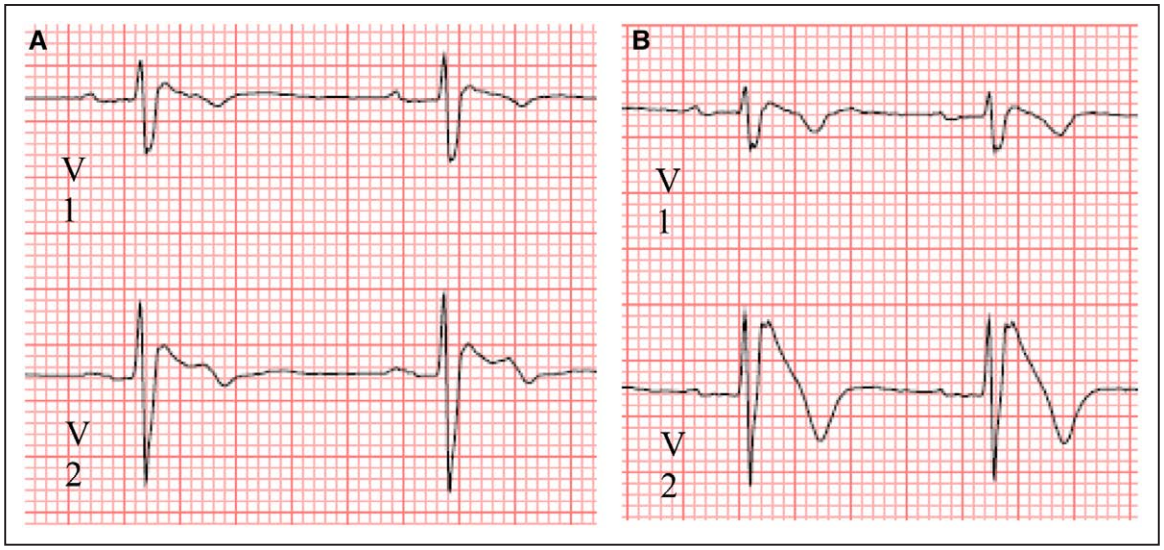

Figure 4. Brugada electrocardiographic pattern unmasked by flecainide.
A, Type 2 Brugada pattern before flecainide. **B**, Same patient on flecainide with type 1 Brugada pattern.

to closely coupled extrasystoles, which can initiate ventricular arrhythmias.[36]

Drug-induced Brugada syndrome is often asymptomatic. However, syncope, VT, and ventricular fibrillation can occur, with symptom onset ranging from weeks to years (but rarely <72 hours) after drug initiation.[37] Fever can precipitate Brugada pattern and trigger ventricular arrhythmias. The overall risk of sudden cardiac death (SCD) resulting from drug-induced Brugada syndrome is ≈ 0.08%/y, lower than that associated with Brugada syndrome.[38]

Treatment of drug-induced Brugada syndrome involves discontinuation of the offending agent. Patients should be screened for Brugada pattern ECG with ambulatory monitoring to exclude latent Brugada syndrome. VT associated with drug-induced Brugada syndrome should be treated with cardioversion/defibrillation or amiodarone. Procainamide should be avoided because it potentiates sodium channel inhibition and can precipitate ventricular arrhythmias. Asymptomatic patients with drug-induced Brugada syndrome should undergo observation without intervention other than avoidance of Brugada syndrome–provoking agents.[24] The role of electrophysiological testing for inducibility of ventricular fibrillation for risk stratification is unclear.[39] An implantable cardioverter-defibrillator may be warranted in patients with prior cardiac arrest, sustained VT, or history of syncope with a spontaneous type I ECG and may be considered for patients with inducible VT during an electrophysiological study.[39] For patients considered for a subcutaneous implantable cardioverter-defibrillator, screening should also be performed during drug challenge to rule out inappropriate sensing and shocks.[40] Epicardial catheter ablation in the right ventricular outflow tract and quinidine are treatment options in selected patients.[24]

Torsades de Pointes

TdP is a polymorphic VT associated with QT prolongation (Figure 5).[24,41,42] TdP may be inherited (congenital long-QT syndrome) or acquired, the most common cause of which is medications. Drugs including terfenadine, astemizole, grepafloxacin, cisapride, and levomethadyl have been withdrawn from the US market and other global markets as a result of TdP-associated deaths. However, >200 drugs remain available with the potential to induce TdP.[43]

Drugs that may provoke TdP are cataloged at the regularly updated QT drugs list that is maintained by the Arizona Center for Education and Research on Therapeutics.[43] This site categorizes QT-prolonging drugs according to whether they are associated with a known, possible, or conditional risk of TdP and whether they should be avoided in patients with congenital long-QT syndrome. QT-prolonging drugs known to cause TdP are presented in Table 7.[43]

The incidence of TdP in the general population is unknown but has been reported to range from 2.5 and 4.0 per 1 million person-years in men and women,[44] respectively, to as high as 4.0 per 100 000 individuals annually.[45] The incidence of TdP among patients in adult intensive care and progressive care units over a 2-month period was 0.07%; 6% of cardiac arrests were caused by TdP.[46] The true incidence of TdP in the general population is difficult to ascertain and likely substantially underestimated as a result of underreporting of cases to pharmacovigilance organizations, absence of a specific code for TdP in the 9th and 10th revisions of the *International Classification of Diseases*,[44] and the fact that many patients with TdP may not survive to reach the hospital.[47] Incidences of TdP associated with specific drugs, when known, are presented in Table 7.

During the initial period of the global severe acute respiratory syndrome coronavirus 2 pandemic in early

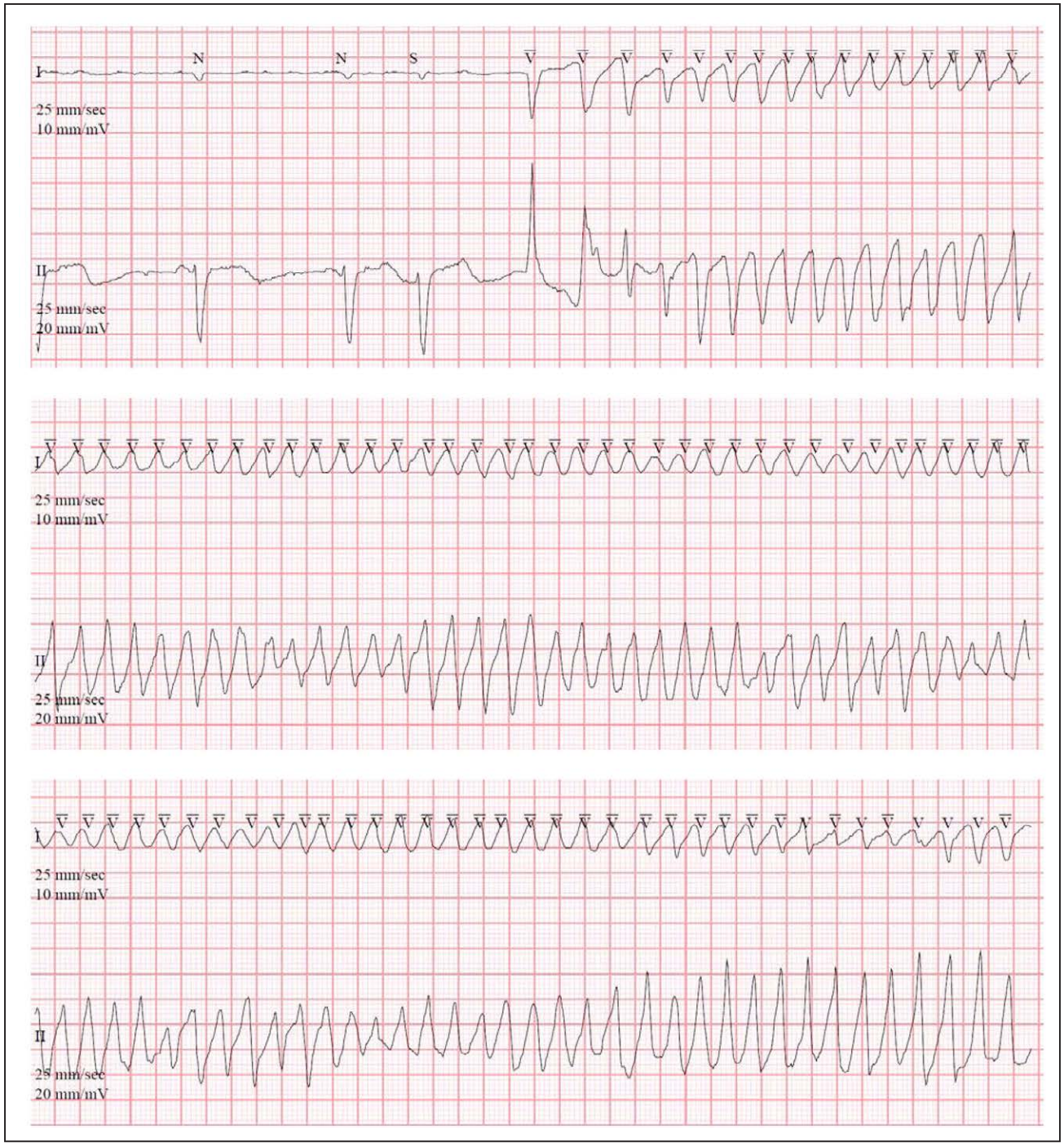

Figure 5. **Torsades de pointes in a patient taking dofetilide (occurred after the second dose).**

2020, chloroquine, hydroxychloroquine, and azithromycin were used widely to manage coronavirus disease 2019 (COVID-19), and the efficacy of these agents for COVID-19 is under investigation in clinical trials. These drugs prolong the QT interval and are known to cause TdP (Table 7).[43,48,49] The incidence of TdP associated with hydroxychloroquine or chloroquine when used to manage COVID-19 is unknown, although TdP has been reported to be associated with hydroxychloroquine alone[50] and in combination with azithromycin in patients with COVID-19.[51,52] The overall incidence of QT interval prolongation associated with hydroxychloroquine or chloroquine is ≈10%,[53] although the incidence increases when azithromycin is added to therapy.[51,54] In addition, other drugs proposed for the management of patients with COVID-19 such as lopinavir/ritonavir may lengthen the QT interval and are associated with a possible risk of TdP.[43] Guidance for managing proarrhythmic risk associated with these drugs in patients with COVID-19 has been published.[48,49]

Table 7. QT Interval–Prolonging Drugs Known to Cause TdP

Drug Class	Drug	Incidence, %	Mechanism
Anesthetic	Propofol	1.93/million	I_{Ks} and I_{to} inhibition
	Sevoflurane	…	
Antiarrhythmic	Amiodarone	0.7–1.5*	I_{Kr} inhibition
	Disopyramide	…	I_{Kr} inhibition
	Dofetilide	1–10†	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Dronedarone	<0.1	I_{Kr} inhibition
	Flecainide	…	I_{Kr} inhibition
	Hydroquinidine	…	I_{Kr} inhibition
	Ibutilide	1.2–11.5	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Procainamide	0.3–6	I_{Kr} inhibition‡
	Quinidine	2–12	I_{Kr}, I_{K1}, and I_{to} inhibition
	Sotalol	0.2–23.6	I_{Kr} inhibition,§ $I_{Na\text{-}L}$ augmentation§
Antibiotic	Azithromycin	0.97‖	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Ciprofloxacin	…	I_{Kr} inhibition
	Clarithromycin	…	I_{Kr} inhibition
	Erythromycin	0.4	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Levofloxacin	0.2	I_{Kr} inhibition
	Moxifloxacin	…	I_{Kr} inhibition
	Roxithromycin	…	I_{Kr} inhibition
Anticancer	Aclarubicin	…	–
	Arsenic trioxide	…	Inhibition of I_{Kr} trafficking
	Oxaliplatin	0.07	…
	Vandetanib	1.4–2.1	I_{Kr} inhibition
Antidepressant (SSRI)	Citalopram	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
	Escitalopram	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
Antiemetic	Domperidone	…	I_{Kr} inhibition
	Droperidol	<0.1	I_{Kr} inhibition
	Ondansetron	…	I_{Kr} inhibition
Antifungal	Fluconazole	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
	Pentamidine	Up to 21	Inhibition of I_{Kr} trafficking
Antimalarial	Chloroquine	…	I_{Kr} inhibition
	Hydroxychloroquine	…	I_{Kr} inhibition
	Halofantrine	…	I_{Kr} inhibition
Antipsychotic	Chlorpromazine	…	I_{Kr} inhibition
	Haloperidol	3.6	I_{Kr} inhibition
	Levomepromazine	…	…
	Levosulpride	…	…
	Pimozide	…	I_{Kr} inhibition
	Sulpiride	…	…
	Sultopride	…	…
	Thioridazine	…	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
Cholinesterase inhibitor	Donepezil	…	I_{Kr} inhibition
Coronary vasodilator	Papaverine HCL	…	I_{Kr} inhibition¶
Illicit	Cocaine	…	I_{Kr} inhibition
Muscle relaxant	Terodiline	…	I_{Kr} inhibition
Opioid agonist	Methadone	…	I_{Kr} inhibition

(*Continued*)

Table 7. Continued

Drug Class	Drug	Incidence, %	Mechanism
Phosphodiesterase-3 inhibitor	Anagrelide	…	…
	Cilostazol	…	…
Psychoactive	Ibogaine	…	I_{Kr} inhibition
Toxin	Cesium chloride	…	I_{Kr} inhibition
Vasoconstrictor	Terlipressin	…	…

HCL, hydrochloride; I_{Kr}, rapid component of delayed rectifier potassium current; I_{Ks}, slow component of delayed rectifier potassium current; I_{K1}, inwardly rectifying potassium current, $I_{Na\text{-}L}$, late sodium current; I_{to}, transient outward potassium current; SSRI, selective serotonin reuptake inhibitor; TdP, torsades de pointes; and …, unknown.

*0.7% to 0.8% with oral administration; 1.5% associated with intravenous administration.

†Incidence is higher in patients with heart failure with reduced ejection fraction and can be as high as 10% if higher-than-recommended doses are administered or if dose is not appropriately adjusted in patients with kidney disease.

‡Primarily by the active metabolite n-acetylprocainamide.

§*d*-Sotalol enantiomer.

‖0.97% of patients with heart rate–corrected QT interval >450 milliseconds during azithromycin therapy.

¶Possibly because of the preservative chlorbutanol.

Drugs cause TdP primarily through inhibition of the rapid component of the delayed rectifier potassium current (I_{Kr}), resulting in action potential duration prolongation and increasing susceptibility to early afterdepolarizations, which can trigger TdP via phase 2 reentry.[24,42,55] Some drugs, including dofetilde, ibutilide, d-sotalol, thioridazine, and erythromycin, also prolong ventricular action potential duration in part through augmentation of late sodium current ($I_{Na\text{-}L}$); for some of these agents, this is due to effects on the phosphoinositide 3-kinase pathway.[56] Action potential duration varies among the ventricular epicardial, midmyocardial, and endocardial myocytes because of differences in ion current densities. The risk of TdP is enhanced in patients with increased transmural dispersion/heterogeneity of repolarization, which can be provoked by many TdP-inducing drugs.[55] In contrast to the antiarrhythmic drugs quinidine and sotalol, amiodarone does not increase dispersion of ventricular repolarization,[57] which may account in part for its somewhat lower incidence of TdP.

The risk of drug-induced prolonged QT interval and TdP has been described with the repolarization reserve concept,[55] which postulates that repolarization is modulated by multiple partially redundant mechanisms, including the balance of function of I_{Kr}, the slow component of the delayed rectifier potassium current (I_{Ks}), $I_{Na\text{-}L}$, and other ion currents. The repolarization reserve theory posits that when 1 determinant of repolarization is abnormal or inhibited, repolarization (and the QT interval) may remain normal or close to normal. However, when an additional perturbation occurs such as the introduction of an I_{Kr}-inhibiting drug, hypokalemia, hypomagnesemia, or other negative repolarization influences, repolarization reserve becomes diminished, resulting in QT prolongation and increasing the risk of TdP.[55]

Although TdP is often transient, self-limiting, and spontaneously terminating, it can degenerate into ventricular fibrillation and cause SCD.[41] Some drugs, including typical and atypical antipsychotic agents and fluoroquinolone and macrolide antibiotics, have been associated with an increased risk of SCD or cardiovascular death, potentially caused by TdP.[2]

Drug-induced TdP is rare in patients without risk factors,[58] which include heart rate–corrected QT interval (QTc) >500 milliseconds or QTc lengthening ≥60 milliseconds from pretreatment value; female sex; age >65 years; bradycardia; acute myocardial infarction; hypokalemia; hypomagnesemia; hypocalcemia; heart failure with reduced ejection fraction; concomitant administration of ≥2 QT-prolonging drugs; history of drug-induced TdP; and conditions leading to elevated plasma concentrations of QT-prolonging drugs such as pharmacokinetic drug-drug interactions, rapid intravenous administration, and inadequate dose adjustment of renally eliminated or hepatically metabolized QT-prolonging drugs in patients with kidney or liver disease. Some patients who experience drug-induced TdP may have a genetic predisposition; nearly 30% of patients who develop drug-induced QT prolongation carry mutations for 1 of the 5 major long-QT syndrome genes, and QT prolongation can become unmasked when these patients receive a QT-lengthening drug.[59] In addition, common genetic variants in aggregate may increase the risk, and a polygenic risk score has been shown to predict drug-induced TdP.[60] However, general genetic screening for prediction of drug-induced TdP is not currently recommended.[24]

The potential for drug-induced TdP may be reduced by correcting modifiable risk factors. In patients taking QT-prolonging drugs, serum potassium and magnesium should be maintained at >4.0 mEq/L and 2.0 mg/dL, respectively.[24,48,49] Concomitant administration of QT-prolonging medications with drugs that inhibit their metabolism should be avoided.[2,41,48,49] Doses of renally eliminated and hepatically metabolized QT-prolonging drugs should be adequately adjusted in patients with kidney or liver disease, respectively.[2]

In patients taking drugs known to cause TdP, particularly those with risk factors, QTc should be monitored

and maintained at <500 milliseconds in the absence of QRS prolongation. Before the initiation of therapy, a baseline ECG should be obtained whenever possible. In hospitalized patients on antiarrhythmic drugs with a known risk for TdP and in those with risk factors for TdP who are taking proarrhythmic non-antiarrhythmic drugs, QT intervals should be monitored daily, preferably with a 12-lead ECG but minimally with a single-lead ECG strip.[61] If available, fully automated QT monitoring, which sounds an alarm if QT prolongation occurs, is recommended.[41] Patients receiving long-term therapy with drugs known to induce TdP should undergo a 12-lead ECG for the measurement of QT intervals every 3 to 6 months, depending on the presence of other risk factors. For patients taking methadone, a baseline ECG should be performed at the time of admission into an opioid treatment program and again within 30 days in those with risk factors. ECGs should be performed annually or when the methadone dose exceeds 120 mg daily. Remote wearable or otherwise portable electrocardiographic monitoring systems hold promise for rendering QT interval monitoring easier and more convenient.[62,63]

Clinical decision support tools have been developed with the objective of reducing TdP risk.[64] At the Mayo Clinic, an institution-wide computer-based QT interval alert system screens all ECGs and alerts physicians to patients with QTc ≥500 milliseconds.[65] Other clinical decision support systems alert prescribers who order QT-prolonging medications for patients with a history of QTc ≥500 milliseconds or who prescribe QT-prolonging drugs for patients with a moderate or high risk of QT interval prolongation according to a validated risk score.[64] Some of these tools minimize the prescribing of QT-prolonging drugs or reduce the risk of QT prolongation.[66]

Management of drug-induced TdP is dependent on distinguishing the arrhythmia from monomorphic VT, non-TdP polymorphic VT, or short-coupled VT.[67] QT-prolonging drugs should be discontinued, and hypokalemia, hypomagnesemia, and hypocalcemia should be corrected.[24] Patients with hemodynamically unstable TdP should undergo defibrillation[24] because shock synchronization may be impossible in patients with polymorphic VT. Intravenous magnesium 1 to 2 g, repeated if necessary, may terminate hemodynamically stable TdP, regardless of the patient's serum magnesium concentration, possibly as a result of the suppression of early afterdepolarizations via calcium channel inhibition. For patients with recurrent TdP associated with bradycardia refractory to intravenous magnesium, overdrive pacing or isoproterenol may terminate TdP by increasing the heart rate and shortening the QT interval.[24] In patients with long-QT syndromes 2 and 3, mexiletine has been shown to shorten the QT interval.[68,69] In patients without long-QT syndrome, oral mexiletine 200 to 450 mg daily may prevent the recurrence of TdP refractory to discontinuation of QT-prolonging drugs, administration of intravenous magnesium, and correction of electrolyte abnormalities.[70] Pretreatment with high-dose magnesium sulfate (5 g over 1 hour) has been used to reduce the risk of TdP associated with ibutilide.[71]

QT Interval Shortening

Short-QT syndrome is a rare congenital channelopathy associated with an increased risk of SCD.[72] Ventricular proarrhythmia or SCD associated with drugs that shorten the QT interval has not been reported in the literature, and there are no published recommendations to avoid QT-shortening medications in this population.[24,73,74] However, it may be prudent to avoid QT-shortening drugs in patients with the short-QT syndrome unless absolutely necessary. Medications that may shorten the QT interval include antiepileptic drugs (primidone, lamotrigine, phenytoin, and rufinamide), digitalis glycosides, class IB antiarrhythmic drugs (lidocaine, mexiletine), and potassium rectifier agents such as pinacidil, levcromakalim, and nicorandil.

SUMMARY AND CONCLUSIONS

Drugs from many therapeutic classes may cause or exacerbate a variety of arrhythmias. Awareness of drugs that may cause arrhythmias and specific arrhythmias that may be drug induced is important. For some drug-induced arrhythmias, attention to risk factors may facilitate prevention and risk reduction. Much remains unknown about the mechanisms of arrhythmias associated with specific drugs. Further research is needed to better define the overall incidence of specific drug-induced arrhythmias, the underlying mechanisms, and the optimal methods to reduce risk and to increase awareness among clinicians and patients. Consideration of the possibility that a patient's arrythmia could be drug-induced is important.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
John D. Fisher	Montefiore Hospital and Medical Center	None	None	None	None	None	Medtronic*	None
Peter J. Schwartz	Istituto Auxologico Italiano IRCCS (Italy)	None	None	None	None	None	None	None
Raymond L. Woosley	University of Arizona College of Medicine–Phoenix	AHRQ (10% effort on research grant)*	None	None	None	None	None	None

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*Modest.

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