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Cardiovascular safety of prokinetic agents: A focus on drug-induced arrhythmias

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Abstract

Background: Gastrointestinal sensorimotor dysfunction underlies a wide range of esophageal, gastric, and intestinal motility and functional disorders that collectively constitute nearly half of all referrals to gastroenterologists. As a result, substantial effort has been dedicated toward the development of prokinetic agents intended to augment or restore normal gastrointestinal motility. However, the use of several clinically efficacious gastropromkinetic agents, such as cisapride, domperidone, erythromycin, and tegaserod, is associated with unfavorable cardiovascular safety profiles, leading to restrictions in their use.

Purpose: The purpose of this review is to detail the cellular and molecular mechanisms that lead commonly to drug-induced cardiac arrhythmias, specifically drug-induced long QT syndrome, torsades de pointes, and ventricular fibrillation, to examine the cardiovascular safety profiles of several classes of prokinetic agents currently in clinical use, and to explore potential strategies by which the risk of drug-induced cardiac arrhythmia associated with prokinetic agents and other QT interval prolonging medications can be mitigated successfully.

Keywords

5-HT₄; adverse drug reactions; cytochrome P450; drug-induced long QT syndrome; gastrointestinal motility; torsades de pointes

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AUTHOR CONTRIBUTIONS

John R. Giudicessi, MD, PhD, performed literature search, drafted and revised the manuscript. Michael J. Ackerman, MD, revised the manuscript. Michael Camilleri, MD, revised the manuscript.

DISCLOSURES

Dr. Ackerman is a consultant for Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia, and St. Jude Medical. Dr. Ackerman and Mayo Clinic are involved in an equity/royalty relationship with AliveCor, Blue Ox Health Corporation, and Stemonix. However, none of these entities were involved in this study in any manner. Dr. Camilleri has received grants to conduct single-center research on prokinetic effects of medications included in this review, including prucalopride, tegaserod, velusetrag, and relamorelin. Dr. Giudicessi declares no conflicts of interest.

1 | INTRODUCTION

Gastrointestinal sensorimotor dysfunction contributes, at least in part, to the pathogenesis of a number of esophageal, gastrointestinal (GI), and colonic disorders.¹ Collectively, GI motility and functional disorders, including chronic diarrhea, esophageal spasm, gastro-esophageal reflux, gastroparesis, and slow-transit constipation, constitute nearly half of all patients referred to gastroenterologists.² Therefore, substantial effort has been dedicated to translating the complex physiologic interplay between gut motor, sensory, and secretory functions into the development of pharmacologic agents capable of restoring normal upper and lower GI motility. These efforts have yielded a number of prokinetic agents, including dopamine receptor antagonists (domperidone and metoclopramide), motilin receptor agonists (azithromycin and erythromycin), and serotonin agonists (such as cisapride, tegaserod, and prucalopride), which have been approved by regulatory bodies for use in clinical practice.

However, the off-target effects of some gastroprokinetic agents, predominantly the unintentional blockade of the *KCNH2*-encoded human Ether-a-go-go-related gene (hERG)/K_v11.1 potassium channels resulted in risk of heart-rate-corrected QT interval (QTc) prolongation, torsades de pointes (TdP), and sudden cardiac death (SCD), prompted the Food and Drug Administration (FDA) to issue a series of “black box” warnings in the 1990s, leading to the restriction or withdrawal of several prokinetic agents due to cardiovascular safety concerns.

In this review, we detail the basic cellular and molecular mechanisms of drug-induced arrhythmias, namely drug-induced long QT syndrome (DI-LQTS); examine the cardiovascular safety profiles of common classes of gastroprokinetic agents; and highlight current and future strategies that can be utilized to mitigate the risk of drug-induced pro-arrhythmia associated with these and other QT interval prolonging medications.

1.1 | Mechanisms of drug-induced arrhythmias

Many common heart rhythms such as bradycardia and first-degree heart block can be triggered by pharmacologic agents. However, the realization that drugs used commonly in the treatment of a wide range of unrelated clinical conditions can prolong the QT interval and confer risk of TdP-associated sudden death has made DI-LQTS one of the most clinically relevant and widely discussed drug-induced cardiac arrhythmias.^{3–7} Like many clinical entities, DI-LQTS is multifactorial in origin and tends to surface in the presence of multiple patient and drug-specific risk factors, some of which are modifiable (electrolyte abnormalities, co-administration of other QT-prolonging agents, and drug accumulation due to renal/hepatic impairment or inhibition of cytochrome P450 metabolism), while others are not modifiable (female sex, underlying genetic disposition, structural heart disease, and diabetes, for example; Table 1).^{8–10} We summarize below current knowledge of the cellular and molecular mechanisms that underlie DI-LQTS.

1.1.1 | Cardiac repolarization: cellular mechanisms and clinical correlates—

The coordinated opening and closing of the cardiac sodium (Na⁺), calcium (Ca²⁺), and potassium (K⁺) channels underlie the inward (depolarizing; Na⁺ and Ca²⁺) and outward

(repolarizing; K^+) currents responsible for the 5 distinct phases of the ventricular cardiac action potential (Figure 1A).¹¹ At the cellular level, a significant increase in depolarizing currents (I_{Na} or $I_{Ca,L}$) or decrease in repolarizing currents (I_{to} , I_{Ks} , I_{Kr} , or I_{K1}) alters the delicate balance of inward and outward currents within individual cardiomyocytes and prolongs the duration of the cardiac action potential (Figure 1B).¹¹ Whenever at least some ventricular action potentials are prolonged, ventricular repolarization time increases as reflected by QT prolongation on the surface electrocardiogram (ECG) (Figure 1C).

As the QT interval is a heart-rate-dependent metric calculation of the heart-rate-corrected QT interval (QTc) from either lead II or V₅ of the 12-lead ECG, using a formula such as Bazett's is required before any intra-individual or inter-individual QT interval comparisons can be made. Current joint American College of Cardiology, American Heart Association, and Heart Rhythm Society guidelines define a prolonged QTc as >450 ms in males and >460 ms in females.¹² However, at least 5%–10% of individuals within the general population have a QTc >460 ms on screening ECG.¹³ Therefore, sex-specific, 99.5th percentile QTc values (>470 ms for males and >480 ms for females) are often used as a cut-off to identify those who would benefit from screening for congenital LQTS. In practice, a baseline QTc value >500 ms is considered definitely abnormal, and a rapid drug-induced QTc increase (Δ QTc) >60 ms is used commonly as a marker of the type of exaggerated QTc response that leads to increased TdP risk in DI-LQTS.¹⁴

Regardless of the ultimate QTc-prolonging mechanism (acquired/drug-induced vs congenital), significant lengthening of the cardiac action potential duration is accompanied by frequent early after depolarizations (EADs) mediated by reactivation of L-type Ca^{2+} and sodium-calcium exchange currents during phases 2 and 3 of the cardiac action potential (ie, ill-timed premature ventricular beats, Figure 1B). In turn, triggered activity from focal EADs coupled with electrical heterogeneity in adjacent regions of myocardium likely generates the conditions needed for unstable reentry and the initiation, propagation, and maintenance of TdP or “twisting of the points,” the hallmark, multi-focal, self-sustaining form of polymorphic ventricular tachycardia associated with LQTS (Figure 1D).¹⁵

1.1.2 | DI-LQTS: history and pathogenesis of a major pharmacologic cardiovascular safety concern—

Although the sentinel description of drug-induced TdP (DI-TdP) occurred in 1964 with the antiarrhythmic drug, quinidine,¹⁶ numerous reports surfaced in the late 1980s and early 1990s that linked a wide range of pharmacologic agents, including antibiotics, antihistamines, antipsychotics, and prokinetic agents, to exaggerated QTc response, DI-TdP, and sudden death. Table 2 summarizes the classes of agents, with those classes actively or previously used by gastroenterologists in bold text, implicated in those reports. Ultimately, rare instances of TdP, in the setting of overdose, hepatic dysfunction, and/or co-prescription of cytochrome P450 family 3 subfamily A member 4 (CYP3A4) inhibitors, such as grape fruit juice and ketoconazole, led to the withdrawal of terfenadine, a non-sedating antihistamine in 1997.^{5,17,18} This was followed by a wave of cardiovascular safety-related drug withdrawals, including the prokinetic agent cisapride.^{19,20} This series of high profile drug withdrawals raised awareness of DI-LQTS among healthcare providers, pharmaceutical companies, and regulatory bodies and brought renewed research interest in elucidating the pathophysiologic mechanisms underlying DI-LQTS.

For the vast majority of drugs causing DI-LQTS and DI-TdP, the underlying pathogenic mechanism was linked, at least initially, to intracellular drug-induced blockade of the rapidly activating component of the phase 3 delayed rectifier K^+ current (I_{Kr}) conducted by hERG/ $K_v11.1$ K^+ channels (Table 2).^{21,22} In turn, I_{Kr} blockade prolongs the cardiac action potential duration/QTc and generates the electrical conditions required for EAD-mediated TdP (Figure 1A-D). The exquisite sensitivity of hERG/ $K_v11.1$ to drug-induced blockade has been attributed to an unusually wide internal cavity or “mouth” located below the narrow K^+ selectivity filter-containing pore that permits access to a large number of drugs. In addition, the presence of multiple aromatic groups within this inner cavity facilitates the formation of covalent π -bonds with these so-called hERG-blocking drugs.²³ However, some drugs (eg, fluoxetine and pentamidine)^{24,25} diminish I_{Kr} current density in vitro through defective trafficking of the hERG/ $K_v11.1$ channel to the cell surface rather than overt disruption of K^+ ion conduction.^{24–26}

Recent evidence suggests that drug-induced blockade of hERG/ $K_v11.1$ channels is not the only mechanism involved in the pathogenesis of DI-LQTS. Another mechanism involves inhibition of phosphoinositide 3-kinase (PI3K) signaling and its downstream effect on multiple depolarizing and repolarizing currents (primarily reduced I_{Kr} and increased late/sustained Na^+ [I_{NaL}] currents) (Figure 1A).²⁷ This mechanism applies to erythromycin (Table 2).²⁸ Interestingly, drugs that also inhibit PI3K/increase I_{NaL} current appear to be more torsadogenic than those that only cause hERG/ $K_v11.1$ blockade.²⁸ Thus, in vitro markers of DI-LQTS risk, most notably the hERG/ $K_v11.1$ half maximal inhibitory concentration (IC_{50}) which is used currently in drug screening during the development process, may underestimate the true DI-LQTS/TdP liability of some pharmacologic agents.

1.2 | Pharmacodynamics and safety profiles of prokinetic agents

Under an ongoing contract with the FDA’s “Safe Use Initiative,” the independent non-profit Arizona Center for Education and Research (AZCERT) actively maintains a professionally curated web-based list of drugs associated with QTc prolongation and TdP (www.crediblemeds.org; also available in mobile app form).²⁹ When coupled with the broader and less reliable FDA Adverse Event Reporting System (FAERS; www.fis.fda.gov),³⁰ which incorporates both direct reports from consumers/healthcare providers and mandatory reports from manufacturers, CredibleMeds and FAERS provide a serviceable means to access postmarketing surveillance data and assess the cardiovascular and overall safety profile of a drug of interest. In the following sections, we briefly review the pharmacodynamics and cardiovascular safety profiles of common classes (dopamine [D_2] receptor antagonists, ghrelin receptor agonists, motilin receptor agonists, and 5-hydroxytryptamine type-4 [5-HT₄] serotonin receptor agonists) of gastroprokinetic agents.

1.2.1 | Dopamine receptor antagonists—Dopamine is a critical neurotransmitter whose release from enteric dopaminergic neurons and subsequent binding to dopamine receptors in GI smooth muscle inhibits motility by reducing gastric peristalsis/tone and intraluminal pressure. Prokinetic agents that block peripheral dopamine (D_2) receptors reduce the inhibitory action of dopamine and accelerate the rate of gastric emptying.^{31,32} Not surprisingly, therefore, the centrally and peripherally acting D_2 receptor antagonist,

metoclopramide (which also functions as a mixed 5-hydroxytryptophan [5-HT; serotonin] type-3 antagonist/5-HT₄ agonist), and the peripherally acting D₂ receptor antagonist, domperidone, demonstrated efficacy in the treatment of foregut dysmotilities, such as gastroparesis, gastro-esophageal reflux, and functional dyspepsia.³³ In addition, given that the area postrema resides outside the blood-brain barrier, D₂ antagonists have concomitant central antiemetic activity through inhibitory action on dopamine receptors within the chemoreceptor trigger zone.³³

At present, metoclopramide is the only FDA-approved drug for gastroparesis and is considered first-line pharmacologic therapy for this purpose.³⁴ However, the use of metoclopramide and other centrally acting D₂ antagonists is complicated by an ~1% risk of extra-pyramidal side effects, which range in severity from mild akathisia to irreversible tardive dyskinesia, when used chronically and/or at high doses.³⁵ Since the FDA affixed a tardive dyskinesia-related “black box” warning in 2009, the use of metoclopramide in the management gastroparesis has declined precipitously.^{35,36}

In contrast, domperidone, which does not readily cross the blood-brain barrier, is not associated with extrapyramidal side effects.³⁷ Due to cardiovascular safety concerns (Table 3), the clinical use of oral domperidone is limited currently to individuals with an FDA Investigational New Drug exemption (ie, treatment-refractory gastroparesis).³² Nevertheless, oral domperidone remains widely available internationally where it is used as an on-label antiemetic and gastroprokinetic agent and off-label galactagogue due to the propensity of dopamine antagonists to elevate serum prolactin levels and cause desired or undesired gynecomastia/galactorrhea.

From a cardiovascular perspective, domperidone and, to a much lesser degree, metoclopramide display an affinity for the hERG/K_v11.1 channel and have been linked to DI-LQTS, TdP, and SCD (Table 3).^{38,39} Domperidone pharmacokinetic studies suggest that the steady-state plasma levels (0.06–0.12 μmol L⁻¹) achieved with a standard 10 mg oral dose frequently meet or exceed the hERG/K_v11.1 IC₅₀ (0.06 μmol L⁻¹; Table 3).^{38,40,41} Therefore, domperidone would be expected to function as a highly potent hERG/K_v11.1 blocker at standard clinical doses. However, an exaggerated QTc response, TdP, and/or SCD are rarely observed clinically with orally administered domperidone or other drugs with similarly narrow hERG/K_v11.1 cardiovascular safety profiles, such as cisapride and the non-sedating antihistamine, terfenadine. This phenomenon is likely explained by vastly lower intra-cardiomyocyte concentrations of these medications due to the combined effects on bioavailability of hepatic drug metabolism (ie, CYP3A family members)⁴² and on intracellular drug accumulation (ie, drug efflux transporter activity, cardiac cytochrome P450 family 2 subfamily J member 2 [CYP2J2] metabolism, etc.).^{43,44} Thus, those rare cases of TdP/SCD linked definitively to oral domperidone, and many of the drugs listed in Table 2 likely represent multifactorial “perfect storms” secondary to the convergence of drug-drug interactions (ie, co-administration of potent CYP3A4 inhibitors), patient-specific risk factors (Table 1), and underlying genetic predisposition (ie, genetic variants that lower cardiac repolarization reserve, impair CYP3A4 metabolism, alter drug efflux, etc.). When occurring together, these multiple factors collectively increase domperidone’s bioavailability and

intracellular accumulation as well as simultaneously lower the patient's cardiac repolarization reserve.

Nevertheless, at the population level, these TdP/SCD “perfect storms” occur frequently enough to drive the observation, across multiple studies, that domperidone is associated with an ~1.5- to 3-fold increased risk of SCD which persists even after covariate adjustment.^{45–47} When combined with recent systematic reviews that question the efficacy of domperidone in the management of GI motility disorders,^{48,49} it should come as no surprise that a recent domperidone risk-benefit assessment³⁹ aligned closely with the FDA's decision to severely restrict the use of domperidone in light of a narrow cardiovascular safety margin that mirrors that of the previously withdrawn prokinetic agent, cisapride.

1.2.2 | Motilin receptor agonists—Motilin is a GI hormone synthesized and secreted by specialized mucosal endocrine cells in the epithelia of the duodenum and gastric antrum during the interdigestive (fasting) state that exists between meals.⁵⁰ The release and binding of motilin to motilin receptors are believed to facilitate acetylcholine release from gut cholinergic motor neurons, thereby indirectly enhancing the amplitude of cholinergically mediated upper GI smooth-muscle contractions during phase III of the migrating motor complex (MMC).^{51,52} These motilin-mediated bursts of forceful high amplitude contractions during phase III of the MMC help clear the upper GI tract of undigested material, prevent bacterial overgrowth, and stimulate the sensation of hunger.^{53,54} Some macrolide antibiotics, namely azithromycin and erythromycin, also function as non-selective motilin receptor agonists that can induce phase III of the MMC and accelerate gastric emptying.^{55–57} In view of these actions, erythromycin and, to a lesser extent, azithromycin are used off-label to rapidly remove gastric contents prior to intubation or endoscopy, facilitate enteral feeding, and treat acutely individuals with a range of GI motility issues such as gastroparesis and chronic intestinal pseudo-obstruction.⁵⁴

Clinically, the chronic use of erythromycin as a gastroprokinetic, even at a dose (125 mg before meals) well below that used for antibiotic purposes (250 to 500 mg every 6 to 12 hours), is hindered by the phenomenon of tachyphylaxis and growing concerns surrounding bacterial resistance and the need for appropriate antibiotic stewardship.⁵⁸ In addition, erythromycin has mild-to-moderate affinity for hERG/K_v11.1,⁵⁹ markedly increases I_{NaL} via PI3K inhibition,²⁸ and, in rare cases, causes exaggerated QTc response, TdP, and SCD (Table 3). Of note, the majority of erythromycin-related TdP/SCD events has occurred during rapid intravenous administration and/or in hosts with 1 additional patient-specific DI-LQTS risk factor (Table 1).⁶⁰

As erythromycin is predominantly metabolized by CYP3A family members,⁶¹ it is not surprising that the small, but increased risk of SCD associated with oral erythromycin administration appears to be driven, in large part, by co-administration of strong CYP3A inhibitors such as azole antifungal agents (eg, fluconazole), protease inhibitors (eg, ritonavir), and non-dihydropyridine calcium channel blockers (eg, diltiazem).⁶² Thus, the rare TdP/SCD adverse events linked definitively to oral erythromycin likely represent similar multifactorial “perfect storms” to those described previously for domperidone.

Azithromycin, which has very weak affinity for hERG/K_v11.1 (Table 3)⁶³ and is not metabolized by CYP3A family members, was long considered to be a safe alternative to QTc-prolonging macrolides such as erythromycin. Thus, the discovery that azithromycin stimulates GI motility via activation of motilin receptors led to speculation that azithromycin might represent the preferred macrolide gastroprokinetic agent due to its favorable cardiovascular safety profile. However, a growing body of epidemiologic and electrophysiological evidence,^{64–67} including the recent description of a azithromycin-induced arrhythmogenic state with a pattern of altered ion currents similar to those seen with PI3K inhibition (Figure 1A),⁶⁷ supports the notion that azithromycin is also potentially torsadogenic, particularly in those individuals with 1 additional cardiovascular/QTc risk factor (Table 1).⁶⁸

1.2.3 | Serotonin receptor agonists—Serotonin (5-HT) is a monoamine neurotransmitter synthesized and stored primarily in the GI tract (~95%) and central nervous system (~5%). In the upper GI tract, serotonin activates 5-HT₄ receptors expressed in enteric neurons and smooth muscle cells.^{69,70} In turn, activated 5-HT₄ receptors facilitate acetylcholine release from myenteric neurons that enhance smooth muscle contractile activity and stimulate GI peristalsis.^{71–74}

Cisapride, a non-selective 5-HT₄ receptor agonist which also functions as a 5-HT₂ and 5-HT₃ receptor antagonist, was approved initially by the FDA for treatment of nocturnal gastro-esophageal reflux in 1993.⁷⁵ However, evidence to support its use in other GI motility disorders was not robust enough to garner additional regulatory approvals. Nevertheless, cisapride was used worldwide for on-label and off-label management of a wide range of GI motility disorders. Initial postmarketing surveillance data suggested that cisapride was both well tolerated and remarkably safe.^{76–79} Yet, by the mid-1990s, rare cases of exaggerated QTc response, TdP, and SCD began to emerge.^{19,80–82} Shortly thereafter, the cellular mechanism behind this pro-arrhythmic potential was linked to potent hERG/K_v11.1 blockade (Table 3) and subsequent risk of DI-LQTS.^{83–85} Furthermore, as cisapride is primarily metabolized by CYP3A family members, marked elevations in plasma concentrations and associated QTc prolongation were observed with co-administration of CYP3A4 inhibitors (fluconazole, ritonavir, grapefruit juice, etc.).^{86,87}

Similar to domperidone and erythromycin, the vast majority of cisapride-associated TdP and SCD occurred with CYP3A4 inhibitor co-administration and/or in individuals with 1 patient-specific DI-LQTS risk factor (Table 1). Despite an initial FDA “black box” warning in 1995 and subsequent expansions in 1996 and 1998 warning of danger posed by the convergence of these patient-specific and drug-specific risk factors, cisapride was withdrawn voluntarily from the world market in 2000, largely due to the documentation of its ongoing inappropriate use.^{88,89}

Tegaserod, a non-selective 5-HT₄ agonist and 5-HT₁ and 5-HT₂ receptor antagonist, received FDA approval for use in the treatment of women with constipation-predominant irritable bowel syndrome in 2002.^{90,91} Unlike cisapride, tegaserod displays weak affinity for hERG/K_v11.1 in vitro,^{90,92} is not extensively metabolized by CYP3A family members,⁹³ and does not cause an exaggerated QTc response or increased risk of TdP (Table 3).⁹⁴

However, in comparison to placebo, tegaserod was associated with a nearly 10-fold (0.01% vs 0.1%) increase in the rate atherosclerotic cardiovascular disease (ASCVD)-related adverse events, such as myocardial infarction, unstable angina, and stroke.⁹¹ Despite a lack of evidence for causality, definitive pathophysiologic mechanism(s), and a subsequent matched case-control study that found no association between tegaserod and ASCVD-related adverse events,⁹⁵ this initial postmarketing surveillance data led the FDA to withdraw tegaserod from the market in 2007.

The withdrawal of the first-generation, non-selective 5-HT₄ receptor agonists, cisapride and tegaserod, due to cardiovascular safety concerns dampened enthusiasm for 5-HT₄ receptor agonists for several years. Recently, there has been renewed interest in the development of more selective, “second-generation” 5-HT₄ receptor agonists. Some have completed or are actively in phase II/III clinical trials (mosapride, naronapride, renzapride, prucalopride, and velusetrag), and a few have received regulatory approval for use outside the United States (mosapride and prucalopride). The clinical uses, efficacy, and non-cardiovascular safety/tolerability of these newer agents have been reviewed in detail elsewhere.^{2,91}

Although postmarketing surveillance data are currently limited or unavailable and the effect on cardiovascular PI3K signaling is unknown, these “second-generation” 5-HT₄ receptor agonists display greater 5-HT₄ selectivity, minimal affinity for hERG/K_v11.1 K⁺ channels, and substantially reduced DI-LQTS/TdP/SCD liability in comparison to their predecessors (Table 3).^{96–99} Thus, 5-HT₄ receptor agonists such as prucalopride and velusetrag show great promise, both from the GI motility therapeutic efficacy and cardiovascular safety perspectives.

1.2.4 | Ghrelin receptor agonists—Ghrelin is a motilin-related peptide released by endocrine cells in the stomach and, to a lesser extent, in the small intestine and colon.¹⁰⁰ Despite divergent tissue distribution and receptor affinities, ghrelin initiates phase III MMC activity and increases gastric emptying during the interdigestive phase in a manner analogous to that of motilin.¹⁰¹ At present, the synthetic ghrelin receptor agonist, relamorelin (RM-131), has entered phase III clinical trials.^{102–104} Importantly, these agents are not extensively metabolized by CYP3A family members, exhibit minimal affinity for hERG/K_v11.1, and have not been associated with overt QTc prolongation.¹⁰⁵ Thus, ghrelin receptor agonists appear to have favorable cardiovascular safety profiles. However, the possibility exists that safety concerns, including cardiac arrhythmias driven by non-hERG/K_v11.1 mechanisms such as PI3K inhibition, could still emerge during the analysis of phase III and early postmarketing surveillance data. Nevertheless, due to a paucity of agents to treat gastroparesis and the efficacy demonstrated in recent phase IIb trials,¹⁰⁴ the FDA has granted a fast track review of relamorelin, and optimism surrounds the prospect that the first ghrelin receptor agonist could be approved for clinical use in the near future.

1.3 | Mitigating the risk of DI-LQTS and DI-TdP associated with prokinetic agents

As illustrated in the sections above, many of the most efficacious prokinetic agents, including cisapride, domperidone, and erythromycin, block hERG/K_v11.1 at high plasma concentrations and, under rare and largely predictable circumstances, lead to an increased

risk of TdP and SCD. Until gastroprokinetic agents with wider cardiovascular safety margins are developed and approved for worldwide use, specific strategies can be utilized to identify those patients and clinical scenarios associated with the highest risk of DI-LQTS/TdP/SCD. In the following sections, we examine the roles that clinical decision support systems (CDSS) and precision genomic medicine may play in assisting healthcare providers to mitigate the small, but increased risk of DI-LQTS/TdP associated with those prokinetic agents in use today.

1.3.1 | Clinical decision support systems and DI-LQTS/TdP prevention—In the case of cisapride, the substantial contributions of patient-specific (ie, female sex, electrolyte abnormalities, structural heart disease, congenital LQTS, renal insufficiency, as summarized in Table 1) and drug-specific (ie, route of administration, co-administration of CYP3A4 inhibitors or other QTc-prolonging medications, potency of hERG/Kv11.1 blockade) risk factors impact the risk of DI-LQTS/TdP, as established and publicized through the series of FDA-mandated “black box” warnings.^{76,88} However, prescribing practices remained essentially unchanged in the wake of this critical new information.⁸⁹

In the era of advanced electronic medical records and medication management systems, substantial effort has been devoted to the development and implementation of CDSS capable of alerting healthcare providers to an array of potentially dangerous clinical scenarios at the point-of-care, including metabolic drug-drug interactions and presence of QTc prolongation. Examples from several institutions, including our own, have demonstrated that the implementation of CDSS that utilizes validated “QTc risk” scorecards^{8,106} composed of independent QTc prolongation risk factors including those listed in Table 1 to identify individuals at highest risk for DI-LQTS/TdP can reduce the inappropriate prescribing of medications with high risk of QTc prolongation and the overall incidence of DI-LQTS.^{107,108} However, similar to FDA “black box” warnings, electronic, institution-wide, CDSS-triggered QTc, and drug-drug interaction alerts can still be ignored and/or misinterpreted by healthcare providers.¹⁰⁹ Nevertheless, in most circumstances, DI-LQTS/TdP risk can be identified and mitigated without the use of CDSS by being hypervigilant to the presence of multiple patient-specific and drug-specific risk factors when determining when and what dose of a prokinetic agent (with known hERG/Kv11.1 blocking potential) to prescribe.

1.3.2 | QTc genetic risk scores: an emerging precision medicine approach to assessing DI-LQTS/TdP risk—Prior genome-wide association studies have shown that common genetic variants account for ~30% of the QTc interval variability/heritability observed in otherwise healthy individuals.^{110–112} Interestingly, a few of the relatively common genetic variants that contribute to QTc prolongation in the general population also independently confer DI-LQTS risk. These include variants in the *KCNE1*-encoded minK K_v7.1 β-subunit^{113,114} and *NOS1AP*-encoded nitric oxide synthetase 1 adaptor protein.¹¹⁵ Not surprisingly, weighted-effect genetic risk scores (GRSs) designed to measure the aggregate effect of multiple QTc-influencing common genetic variants^{110,116} can identify those individuals at greatest risk of developing an exaggerated QTc response/TdP following exposure to known QT-prolonging drugs.^{117,118} Thus, one can envision how the preemptive use of QTc GRSs, in combination with CDSS and additional pharmacogenomics testing,

may help someday to further individualize the selection of drug and the dose of medications known to prolong the QTc, including commonly used prokinetic agents such as domperidone and erythromycin.

2 | CONCLUSION

As illustrated in this review, many of the prokinetic agents approved for the management of GI motility disorders carry a small but increased risk of drug-induced arrhythmia. Epidemiologic studies have identified many important patient-specific and drug-specific risk factors that, when present, typically in combination, exponentially increase the risk of DI-LQTS/TdP. Prior to drug administration, careful weighing of these risk factors (ie, calculation of clinical QTc risk scores) against the potential therapeutic benefits of a prokinetic agent with known QT-prolonging potential can substantially decrease, but not entirely eliminate the risk of DI-LQTS/TdP. Unfortunately, many gaps still exist and require further research, including (i) the full extent of PI3K signaling inhibition as a contributor to DI-LQTS pathogenesis, (ii) the most effective means of using clinical and genomic risk factors to identify those at greatest DI-LQTS/TdP risk, (iii) the value of intensive inpatient and outpatient QTc monitoring (ie, the use of wearable/handheld technology) in early DI-LQTS identification, and (iv) the adjunct use of QTc shortening drugs (ie, lidocaine/mexiletine) in high-risk patients who require QTc-prolonging medications. Hopefully, ongoing efforts to address these critical gaps, as well as to develop “next-generation” prokinetic agents with wider cardiovascular safety margins, will assure that patients with a wide range of GI motility and functional issues continue to receive the most efficacious and safe pharmacotherapy possible.

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Abbreviations:

5-HT₄	5-hydroxytryptophan type-4 receptor
ASCVD	atherosclerotic cardiovascular disease
Ca²⁺	calcium
CDSS	clinical decision support systems
CYP3A4	cytochrome P450 family 3 subfamily a member 4
DI-LQTS	drug-induced long QT syndrome
DI-TdP	drug-induced torsades de pointes
EAD	early after depolarization

ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
GRS	genetic risk score
hERG	human Ether-a-go-go-related gene potassium channel
I_{Kr}	rapidly activating component of the delayed rectifier potassium current
I_{NaL}	late/sustained sodium current
K^+	potassium
LQTS	long QT syndrome
MMC	migrating motor complex
Na^+	sodium
PI3K	phosphoinositide 3-kinase
QTc	heart-rate-corrected QT interval
SCD	sudden cardiac death
TdP	torsades de pointes

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Key Points

- Many prokinetic agents carry a small but increased risk of drug-induced arrhythmia.
- This review details the mechanisms underlying drug-induced QT prolongation, examines the cardiovascular safety profiles of common prokinetic agent classes, and highlights strategies to mitigate the risk of arrhythmia associated with prokinetic agents.
- Until prokinetic agents with more favorable cardiovascular safety profiles are developed and approved for worldwide use, awareness of patient- and drug-specific risk factors can help mitigate the risk of drug-induced arrhythmia.

FIGURE 1.

Current paradigm for the pathogenesis of drug-induced long QT syndrome (DI-LQTS). (A) Drug binding within the inner mouth of the hERG/K_v11.1 potassium channel results in a reduction of I_{Kr} current. Alternatively or concurrently, inhibition of phosphoinositol 3-kinase decreases phosphatidylinositol 3,4,5-triphosphate (PIP₃)-mediated downstream signaling, predominantly resulting in an increase in late I_{Na} and decrease in I_{Kr} current. (B) An increase in outward depolarizing currents (purple channels/boxes) and/or decrease in inward repolarizing currents (orange channels/boxes) prolongs the action potential duration (APD), generating the substrate needed for an increased frequency of early after depolarizations (EADs). (C) An increase in APD manifests as heart-rate-corrected QT (QTc) interval prolongation on 12-lead surface electrocardiogram. (D) EAD-triggered action potentials can precipitate torsades de pointes (TdP) which may degenerate into ventricular fibrillation

TABLE 1

Modifiable and non-modifiable risk factors for drug-induced long QT syndrome/torsades de pointes^a

<i>Modifiable risk factors</i>	
Electrolyte disturbances	
Hypocalcemia (<4.65 mg/dL)	
Hypokalemia (<3.4 mmol/L)	
Hypomagnesemia (<1.7 mg/dL)	
QT-prolonging medication polypharmacy	
Concurrent use of 1 medication from www.azcert.com (www.crediblemeds.com)	
<i>Non-modifiable risk factors</i>	
Common diagnoses	
Acute coronary syndrome	
Anorexia nervosa or starvation	
Bradyarrhythmias <45 bpm	
Cardiac heart failure (ejection fraction <40%; uncompensated)	
Congenital long QT syndrome or other genetic susceptibility	
Chronic renal failure requiring dialysis	
Diabetes mellitus (types 1 and 2)	
Hypertrophic cardiomyopathy	
Hypoglycemia (documented and in the absence of diabetes)	
Pheochromocytoma	
Status post cardiac arrest (within 24 h)	
Status post syncope or seizure (within 24 h)	
Stroke, subarachnoid hemorrhage, or other head trauma (within 7 d)	
Clinical history	
Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis	
Demographic	
Elderly (>65y of age)	
Female gender	

^a A “pro-QTc” score 4 based on risk factors similar to those listed above was an independent predictor of mortality in patients with QT interval prolongation.⁸ Unfortunately, the predictive value of these risk factors in patients with normal or borderline QT intervals has not been assessed.

TABLE 2

Representative pharmacologic agents (listed by therapeutic class) associated with drug-induced long QT syndrome/torsades de pointes (functional GI/motility drugs are shown in bold)

Drug	hERG/ I_{K_r} block-mediated	Enhanced I_{NaL} -mediated	Reference(s)
Antiarrhythmics			
Dofetilide	+	+	[28,119,120]
Quinidine	+	Unknown	[121]
Sotalol	+	+	[28,122]
Antibiotics			
Fluoroquinolones ^a	+	– ^c	[28,123]
Macrolides^a	+	+ ^d	[28,67,124]
Antidepressants			
Citalopram/Escitalopram	+	Unknown	[125]
Antiemetics			
Domperidone^b	+	Unknown	[38]
Ondansetron	+	Unknown	[126]
Antifungals			
Fluconazole	+	Unknown	[127]
Pentamidine	+	Unknown	[25]
Antihistamines			
Astemizole ^b	+	Unknown	[128]
Terfenadine ^b	+	+	[27,128]
Antineoplastics			
Arsenic trioxide	+	Unknown	[129]
Nilotinib	+	+	[27,130]
Antipsychotics			
Haloperidol	+	Unknown	[131]
Pimozide	+	Unknown	[132]
Thioridazine	+	Unknown	[133]
Cholinesterase inhibitors			
Donepezil	+	Unknown	[134]
Prokinetics			
Cisapride^b	+	Unknown	[22]
Opioid agonists			
Methadone	+	Unknown	[135]

hERG, human Ether-a-go-go-related gene potassium channel; PI3K, phosphoinositide 3-kinase.

^aMultiple fluoroquinolone (ciprofloxacin, gatifloxacin^b, grepafloxacin^b, levofloxacin, moxifloxacin, sparfloxacin^b) and macrolide (azithromycin, clarithromycin, erythromycin, and roxithromycin^b) antibiotics known to cause DI-LQTS/TdP.

^bThe following agents have failed to gain approval or been withdrawn from the United States and/or Worldwide market due to cardiovascular safety concerns related to DI-LQTS/TdP.

^cThe study by Yang et al²⁸ demonstrated that moxifloxacin had no effect on PI3K/ I_{NaL} . It is unknown whether this observation is limited to moxifloxacin or represents a fluoroquinolone class effect.

^dBoth erythromycin and azithromycin have been shown to increase peak I_{Na} and/or I_{NaL} . However, the effect of clarithromycin on PI3K/ I_{NaL} remains unknown.

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TABLE 3

Comparison of potency of hERG/Kv11.1 (I_{Kr}) blockade and number of serious postmarketing adverse events for gastroprokinetic agents with active or prior regulatory approval

Prokinetic agent	Potency of hERG block	Credible meds classification	VT/VF/TdP/LQTS in FAERS (deaths) ^d	Cardiac arrest in FAERS (deaths) ^d	Total serious events in FAERS (deaths) ^d	Refs.
D ₂ receptor antagonists						
Clebopride	High	Not listed	0(0)	0(0)	6(1)	[29,30,136]
Domperidone ^a	High	Known TdP risk	47 (13)	23 (20)	1,485 (202)	[29,30,38]
Metoclopramide	Moderate	Avoid in cLQTS	67(2)	105 (55)	17,356 (1,129)	[29,30,38]
Motilin receptor agonists						
Azithromycin	Low ^c	Known TdP risk	4(0)	1(0)	116 (4)	[29,30,63]
Erythromycin	Low ^c	Known TdP risk	206 (33)	95 (36)	5,825 (503)	[29,30,59]
5-HT ₄ receptor agonists						
Cisapride ^b	High	Known TdP risk	808 (115)	439 (135)	6,671 (900)	[29,30,84]
Mosapride ^a	NE	Not listed	0(0)	0(0)	28(5)	[29,30,98]
Prucalopride ^a	Low	Not listed	0	0	27(0)	[29,30,98]
Tegaserod ^b	Low	Not listed	1(0)	5(4)	719 (89)	[29,30,90]

FAERS, Food and Drug Administration Adverse Event Reporting System; hERG, human Ether-a-go-go-related gene; IC₅₀, half maximal inhibitory concentration; and NE, no effect.

^a Agents currently not available in the United States.

^b Cisapride (risk of TdP) and tegaserod (risk of myocardial infarction) were withdrawn from the United States and International market.

^c With chronic use, both azithromycin and erythromycin, may be associated with increase late sodium current (I_{NaL}), potentially related to inhibition of cardiac PI3K signaling. Thus, the potency of hERG/Kv11.1 block likely underestimates the true risk of DI-LQTS/TdP associated with these agents.

^d Adverse event reporting from postmarketing surveillance does not account for prescription volume and is often subjected to significant bias from confounding variables, quality of reported data, duplication, and underreporting of events.