Salient Journal of Cardiology
Review Article (ISSN 2994-774X)

Drug-Induced Long QT Syndrome and Torsades de Pointes: A Cardiological Review of Mechanisms, Risk Stratification, and Clinical Management

Muhammad Salman Abu Bakar Janjua[1], Hafsa Khizar[2], Marwa Tufail[2], Muhammad Tashfeen Chishti[2], Muhammad Syed Ali Akbar Rizvi[2], Muhammad Sheraz[3*], Ujala Ahmed[4], Fiza Fazeela[5]

[1]Bolan Medical College, Quetta

[2]Multan Medical & Dental College, Multan

[3]Nishtar Medical University, Multan

[4]Hamdard University Hospital, Karachi

[5]Chandka Medical College, Larkana

Citation: *Muhammad Salman Abu Bakar Janjua, Hafsa Khizar, Marwa Tufail, Muhammad Tashfeen Chishti, Muhammad Syed Ali Akbar Rizvi, Muhammad Sheraz, Ujala Ahmed, Fiza Fazeela. Drug-Induced Long QT Syndrome and Torsades de Pointes: A Cardiological Review of Mechanisms, Risk Stratification, and Clinical Management. Sali Jour Cardi. 2023;5(5):1-7.*

Received Date: 24 May, 2026; **Accepted Date:** 25 May, 2026; **Published Date:** 26 May, 2026

***Corresponding author:** Muhammad Sheraz, Nishtar Medical University, Multan

Drug-induced long QT syndrome (diLQTS) is an acquired cardiac electrophysiological disorder characterized by prolongation of the corrected QT (QTc) interval on electrocardiography (ECG), which predisposes patients to torsades de pointes (TdP), a polymorphic ventricular tachyarrhythmia that can degenerate into ventricular fibrillation and cause sudden cardiac death.[1–3] It is among the most clinically significant yet preventable causes of malignant arrhythmias in both inpatient and outpatient settings.[4] The condition is particularly relevant in modern medicine due to widespread use of QT-prolonging drugs across cardiology, psychiatry, infectious diseases, and oncology.

This review discusses the molecular mechanisms, pharmacological triggers, clinical risk stratification, and evidence-based management strategies for diLQTS and TdP.

Molecular and Electrophysiological Mechanisms

The primary mechanism underlying drug-induced QT prolongation is inhibition of the rapid component of the delayed rectifier potassium current (Ikr), which is mediated by the human ether-à-go-go-related gene (hERG) potassium channel.[5–7] This channel plays a critical role in phase 3 repolarization of the cardiac action potential. Blockade of hERG channels prolongs ventricular repolarization, thereby increasing the duration of the action potential and the QT interval on ECG.[8]

Delayed repolarization promotes the development of early afterdepolarizations (EADs), which are abnormal depolarizations occurring during phases 2 or 3 of the action potential.[9] EADs are particularly likely under

conditions of bradycardia or prolonged pauses, which further extend repolarization time. These triggered events may initiate premature ventricular complexes that fall on the T wave ("R-on-T phenomenon"), serving as a trigger for TdP.[10]

In addition to ion channel effects, heterogeneity of myocardial repolarization across the ventricular wall contributes significantly to arrhythmogenesis. Increased transmural dispersion of repolarization creates a substrate for re-entry circuits, facilitating sustained polymorphic ventricular tachycardia.[11]

Interestingly, not all QT-prolonging drugs carry the same arrhythmogenic risk. Amiodarone, for example, prolongs QT significantly but rarely causes TdP due to its multichannel blocking effects, which homogenize repolarization.[12] In contrast, selective hERG blockers produce marked dispersion and are more strongly associated with TdP.[13]

Drugs Implicated in QT Prolongation

A wide range of medications across multiple therapeutic classes are associated with QT prolongation and TdP risk. These include:

* Class IA and III antiarrhythmics (quinidine, sotalol, dofetilide)
* Macrolide antibiotics (erythromycin, clarithromycin)
* Fluoroquinolones (moxifloxacin, levofloxacin)
* Antipsychotics (haloperidol, ziprasidone, quetiapine)
* Antidepressants (citalopram, tricyclic antidepressants)
* Antiemetics (ondansetron, domperidone)
* Antifungals (fluconazole, ketoconazole)
* Opioid replacement therapy (methadone)
* Anticancer agents (tyrosine kinase inhibitors, arsenic trioxide)[14–17]

Risk is often dose-dependent; however, clinically significant QT prolongation may occur at therapeutic doses, particularly in patients with multiple risk factors or drug interactions affecting metabolism via CYP450 enzymes.[18]

Several drugs have historically been withdrawn or restricted due to TdP risk, highlighting the importance of post-marketing pharmacovigilance systems.[19]

Risk Factors for Torsades de Pointes

TdP occurs due to a complex interaction between drug exposure and patient susceptibility. It is rarely caused by a single factor alone.

Patient-related risk factors include:

* Female sex (higher baseline QTc and increased drug sensitivity)

* Advanced age (>65 years)
* Structural heart disease (heart failure, myocardial infarction, cardiomyopathy)
* Bradycardia or conduction disease
* Congenital long QT syndrome or subclinical channelopathies
* Renal or hepatic impairment leading to drug accumulation
* Genetic polymorphisms affecting ion channels or drug metabolism[20–23]

Acquired and iatrogenic risk factors include:
* Hypokalemia, hypomagnesemia, hypocalcemia
* Concomitant use of multiple QT-prolonging drugs
* High drug plasma concentration
* Drug-drug interactions inhibiting CYP3A4 or CYP2D6
* Acute systemic illness (sepsis, stroke, starvation states) [24]

Electrolyte disturbances play a particularly important role by enhancing Ikr blockade and increasing membrane excitability. Hypokalemia, even within low-normal range, significantly increases TdP risk.[25]

Clinical Presentation and ECG Features

Patients with TdP typically present with palpitations, dizziness, syncope, presyncope, or sudden cardiac arrest. Episodes may be self-terminating or may deteriorate into ventricular fibrillation.[26]

ECG findings include:
* Prolonged QTc interval (>450 ms in males, >470 ms in females)
* Marked risk when QTc >500 ms or increase >60 ms from baseline
* Polymorphic ventricular tachycardia with characteristic twisting QRS complexes around the isoelectric line [27]

TdP is often initiated by a premature ventricular beat following a pause or bradycardia, supporting the importance of heart rate as a modulator of arrhythmia risk.[28]

Risk Stratification Tools

Risk stratification is essential in hospitalized patients receiving QT-prolonging drugs. The Tisdale risk score is widely used in critical care settings and incorporates variables such as age, sex, baseline QTc, electrolyte levels, diuretic use, sepsis, and number of QT-prolonging medications.[29]

Patients are generally classified as:
* Low risk (<7 points)
* Moderate risk (7–10 points)
* High risk (>11 points)

A QTc exceeding 500 ms is consistently associated with significantly increased risk of TdP and should prompt

immediate intervention.[30]

Continuous ECG monitoring is recommended for high-risk patients, particularly in intensive care units or during initiation of high-risk medications.

Prevention Strategies

Prevention is the most effective strategy in managing diLQTS. Key preventive measures include:

1. Baseline ECG before initiating QT-prolonging therapy
2. Regular QTc monitoring in high-risk patients
3. Avoidance of drug combinations with additive QT effects
4. Correction of electrolytes, especially potassium and magnesium
5. Dose adjustment in renal or hepatic impairment
6. Use of alternative non-QT-prolonging agents when available
7. Awareness of drug-drug interactions involving CYP450 inhibition[31]

Electronic prescribing systems with automatic QT alerts and pharmacist-led medication review programs have demonstrated significant reductions in preventable diLQTS events.[32]

Acute Management of Torsades de Pointes

TdP is a medical emergency requiring immediate intervention. The first step is discontinuation of the offending drug and correction of reversible factors.

First-line therapy:

Intravenous magnesium sulfate is the treatment of choice, even in patients with normal serum magnesium levels.[33] Magnesium stabilizes myocardial cell membranes and suppresses early afterdepolarizations.

Additional interventions:

* Correction of hypokalemia to high-normal range (4.5–5.0 mmol/L)
* Temporary transvenous or transcutaneous pacing to increase heart rate and shorten QT interval
* Isoproterenol infusion in acquired bradycardia-related TdP (not in congenital LQTS)[34]

Electrical cardioversion:

Indicated for hemodynamically unstable or sustained TdP progressing to ventricular fibrillation.

Prompt recognition and early treatment are critical, as TdP can deteriorate rapidly into fatal arrhythmias.

Long-Term Management and Prognosis

Long-term management involves strict avoidance of the offending agent and education regarding QT-prolonging drugs. Patients should be counselled about over-the-counter medications and herbal supplements that may affect cardiac repolarization.

Patients with suspected underlying congenital long QT syndrome should undergo cardiology evaluation, genetic testing, and family screening when appropriate.[35]

Beta-blockers may be indicated in congenital cases or in patients with recurrent arrhythmias. Implantable cardioverter-defibrillator (ICD) therapy is reserved for high-risk or refractory cases.

Overall prognosis is favorable when the condition is promptly recognized and treated. However, delayed diagnosis remains a major cause of preventable sudden cardiac death, especially in psychiatric, elderly, and intensive care populations.[36]

CONCLUSION

Drug-induced long QT syndrome and torsades de pointes represent a critical intersection of pharmacology, electrophysiology, and clinical medicine. The fundamental mechanism involves hERG potassium channel blockade leading to delayed repolarization and triggered ventricular arrhythmias. However, arrhythmia development depends heavily on patient-specific risk factors such as electrolyte imbalance, comorbid disease, and polypharmacy.

Prevention through rational prescribing, ECG monitoring, and correction of metabolic disturbances remains the cornerstone of management. Acute TdP requires rapid administration of intravenous magnesium and stabilization of cardiac rhythm. Increased clinician awareness and systematic risk stratification can significantly reduce morbidity and mortality associated with this entirely preventable condition.

REFERENCES

1. Roden DM. Drug-induced prolongation of the QT interval. Circulation. 2004;109(12):1537–1543.
2. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J. 2007;153(6):891–899.
3. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Drug Saf. 2012;35(5):343–356.
4. Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM, Priori SG, et al. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electrophysiol. 2004;15(4):475–495.
5. Vandenberg JI, Perry MD, Perrin MJ, Mann SA, Ke Y, Hill AP. hERG K+ channels: structure, function, and clinical significance. Heart Rhythm. 2012;9(8):1325–1332.
6. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. Nature. 2006;440(7083):463–469.
7. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104(4):569–580.
8. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac

death syndromes. J Am Coll Cardiol. 2007;49(13):1435–1450.

9. El-Sherif N, Turitto G. Torsade de pointes. Heart Rhythm. 2011;8(8):137–145.
10. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation. 1996;93(2):372–379.
11. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the long QT syndrome. J Am Coll Cardiol. 1999;34(1):218–225.
12. Hondeghem LM. QT prolongation is an unreliable predictor of ventricular arrhythmia. Cardiovasc Res. 2008;77(3):512–520.
13. Yap YG, Camm AJ. Drug-induced QT prolongation and torsades de pointes. Lancet. 2003;361(9364):1425–1431.
14. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and American College of Cardiology Foundation. Circulation. 2010;121(8):1047–1060.
15. Woosley RL, Heise CW, Gallo T, Tate J, Woosley D, Romero KA. QTdrugs List. AZCERT, Inc. Available from: CredibleMeds Official Website
16. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in risk assessment, prevention and management. Can J Hosp Pharm. 2016;69(4):189–197.
17. Salem JE, Alexandre J, Bachelot A, Funck-Brentano C. Influence of pharmacogenetics on drug-induced QT interval prolongation and torsades de pointes. Circulation. 2016;134(13):1000–1005.
18. Shah RR. Drug-induced QT interval prolongation—regulatory guidance and perspectives on hERG channel studies. Br J Clin Pharmacol. 2002;54(2):188–202.
19. Roden DM. Keep the QT interval: it is a reliable predictor of ventricular arrhythmias. N Engl J Med. 2008;358(2):1881–1890.
20. Schwartz PJ, Ackerman MJ, George AL Jr, Wilde AAM. Impact of genetics on the clinical management of channelopathies. Eur Heart J. 2012;33(15):182–185.
21. Moss AJ. Long QT syndrome. N Engl J Med. 2003;349(19):1772–1782.
22. Viskin S. Long QT syndromes and torsade de pointes. Lancet. 1999;354(9190):1625–1633.
23. Priori SG, Wilde AAM, Horie M, Cho Y, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on inherited primary arrhythmia syndromes. Eur Heart J. 2015;36(41):2793–2801.
24. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is “normal”. Circulation. 2008;117(23):218–225.
25. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Heart Rhythm. 2011;8(8):137–145.
26. Chiang CE. Congenital and acquired long QT syndrome: current concepts and management. Cardiol Rev. 2004;12(4):201–207.
27. Passman R, Kadish A. Polymorphic ventricular tachycardia, long QT syndrome, and torsades de pointes. Ann Intern Med. 2001;134(11):1029–1036.
28. Viskin S, Halkin A, Roth A, Zeltser D, Justo D, Glikson M, et al. Quinidine, torsades de pointes, and sudden death. Heart Rhythm. 2005;2(6):642–649.
29. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and

validation of a risk score to predict QT interval prolongation in hospitalized patients. J Am Heart Assoc. 2013;2(6):e000152.

30. Schwartz PJ, Woosley RL. Predicting the unpredictable: drug-induced QT prolongation and torsades de pointes. Eur Heart J. 2013;34(27):2053–2058.
31. Drew BJ, Harris P, Zègre-Hemsey JK, Mammone T, Schindler D, Salas-Boni R, et al. Insights into prevention of torsade de pointes in hospitalized patients. Crit Care Med. 2014;42(3):489–497.
32. Tisdale JE, Miller DA, Kowey PR. Drug-induced arrhythmias: a scientific review of risk assessment and prevention. Pharmacotherapy. 2013;33(8):810–821.
33. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Stern S. Treatment of torsade de pointes with magnesium sulfate. Am J Cardiol. 1988;62(1):37–41.
34. Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, et al. Inaccurate electrocardiographic interpretation of long QT syndrome. Heart Rhythm. 2005;2(6):642–649.
35. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death. Eur Heart J. 2015;36(41):2793–2867.
36. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. J Am Coll Cardiol. 2011;57(8):943–950.