

Additive QTc Prolongation with Concurrent Use of Bedaquiline, Clofazimine, and Fluoroquinolones in MDR-TB: Role of Hypokalemia and Hypomagnesemia as Modifying Risk Factors

M Hariprasad Kamath^a, Disha Shetty^a, Amruth Kiran^b, Manjunath Shetty^b, Arul Amuthan^b, Devasrita Dash^b, Tatiyana Mandal^b, K Ganesh Shenoy^{b,*}

M Hariprasad Kamath^a, Disha Shetty^a, Amruth Kiran^b, Manjunath Shetty^b, Arul Amuthan^b, Devasrita Dash^b, Tatiyana Mandal^b, K Ganesh Shenoy^{b,*}

^aDepartment of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Madhav Nagar, Manipal – 576104, Karnataka, INDIA.

^bDepartment of Basic Medical Sciences, Manipal Academy of Higher Education, Madhav Nagar, Manipal – 576104, Karnataka, INDIA.

Correspondence

Dr. K Ganesh Shenoy

Assistant Professor, Selection Grade, Division of Pharmacology, Department of Basic Medical Sciences, Manipal Academy of Higher Education, Madhav Nagar, Manipal – 576104, Karnataka, INDIA.

E-mail: kg.shenoy@manipal.edu

History

- Submission Date: 05-05-2026;
- Review completed: 21-07-2026;
- Accepted Date: 25-08-2026.

DOI : 10.5530/pj.2026.18.154

Article Available online

<http://www.phcogj.com/v18/i3>

Copyright

© 2026 Phcogj.Com. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.

ABSTRACT

Introduction: Oral medications for the treatment of MDR-TB regimens, including bedaquiline, clofazimine, and moxifloxacin, are increasingly prescribed globally. These drugs can lead to increased QTc intervals and ventricular arrhythmias. The risk increases when these medications are combined, as per WHO guidelines. Electrolyte imbalance, common in malnourished MDR-TB patients, can exacerbate this issue. **Objective:** This narrative review synthesizes available evidence to characterize the additive QTc-prolongation risk of the bedaquiline–clofazimine–moxifloxacin combination and delineate the specific contributions of electrolyte imbalance as a risk factor. **Methods:** A narrative review was conducted using databases such as PubMed, Scopus, Embase, and ClinicalTrials.gov. **Results:** The concurrent use of bedaquiline, clofazimine, and moxifloxacin is associated with additive QTc prolongation of approximately 35–50 ms in many patients, depending on regimen, drug exposure, and patient characteristics. In MDR-TB patients, hypokalemia is associated with QTc prolongation, and lower serum potassium levels may increase the risk of clinically significant QT interval prolongation. Hypomagnesemia compounds this risk by driving refractory potassium depletion through impaired Na⁺/K⁺-ATPase channel. Together, patients with borderline baseline QTc and untreated electrolyte disturbances may push QTc beyond the critical 500 ms threshold. **Conclusion:** Correcting the potassium and magnesium levels might become a clinically valuable approach to prevent cardiac events associated with QTc prolongation in patients with MDR-TB along with electrocardiogram monitoring in line with WHO recommendations, is a key component of successful treatment.

Keywords: bedaquiline; clofazimine; moxifloxacin; QTc prolongation; MDR-TB; electrolyte imbalance

INTRODUCTION

Among the major challenges associated with infectious diseases worldwide, multidrug-resistant tuberculosis (MDR-TB) remains relevant. According to the World Health Organization (WHO), approximately 3,90,000 new cases of MDR-TB were registered in 2024, while the global success rate of therapy was around 71%¹. During the past decade, there has been innovative development in the field of MDR-TB therapeutics because of the registration of bedaquiline in 2012 and further restructuring of treatment into all-oral drug regimens free of injectable antibiotics². Current regimens of WHO-recommended therapies for MDR-TB, such as the bedaquiline-pretomanid-linezolid-moxifloxacin (BPaLM) regimen and short standardized bedaquiline-clofazimine-based regimens, significantly improve therapeutic results³.

However, this positive trend highlights an additional concern related to the cardiac safety of the therapy. It is associated with the coadministration of drugs that prolong the QTc interval by inhibiting the hERG-encoded potassium current (IKr), such as bedaquiline, clofazimine, and fluoroquinolones, including moxifloxacin. The simultaneous prescription of these classes of drugs, which is seen in some recommended regimens, poses the risk

of additive QTc prolongation. The QTc interval, which is measured during electrocardiography and represents the corrected ventricular repolarization time, can exceed 500 ms and predisposes patients to early afterdepolarizations (EADs), resulting in Torsades de Pointes (TdP)^{4,5}.

The interplay between pharmacological risk factors and biological susceptibility in MDR-TB is exemplified in the case of the latter patients. Nutritional deficiencies, diarrhea, nausea, and vomiting resulting from other drugs, including ethionamide and linezolid, and the catabolic response to actively infected TB contribute to an increase in the incidence of electrolyte imbalances⁶. Hypokalemia and hypomagnesemia, individually and in combination, further potentiate the occurrence of drug-induced QTc prolongation through electrophysiological mechanisms. However, electrolyte imbalances are often overlooked and are limited in resource-constrained settings, especially in Low- and Middle-Income Countries (LMICs)⁷.

While awareness regarding the risks posed to QTc intervals by MDR-TB regimens has increased, data concerning the contribution of electrolyte alterations in the form of potential modifiable risk factors for drug-induced QTc prolongation in such a setting are lacking. In addition, no prospective study has been conducted to assess the interactive

Cite this article: Hariprasad K M, Disha S, Amruth K, Manjunath S, Arul A, Devasrita D, Tatiyana M, Ganesh S K. Additive QTc Prolongation with Concurrent Use of Bedaquiline, Clofazimine, and Fluoroquinolones in MDR-TB: Role of Hypokalemia and Hypomagnesemia as Modifying Risk Factors. Pharmacogn J. 2026;18 (3): 348-357.

effect between electrolytes and triple QTc-prolonging drugs on the repolarization process. This narrative review seeks to fill this gap in the literature and analyze how the concurrent presence of hypokalemia and hypomagnesemia affects the additive risk of bedaquiline-clofazimine-fluoroquinolone combinations in prolonging QTc intervals.

The novelty of this article is its comprehensive exploration of the additive or synergistic effects of the drug combinations used in the MDR-TB, namely bedaquiline, clofazimine, and moxifloxacin, which lead to QTc prolongation due to electrolyte imbalance. Unlike previous reviews, which might have addressed QT prolongation associated with individual drugs or broader drug classes, this narrative review specifically describes how these medications interact synergistically to exacerbate QTc prolongation, emphasizing the importance of patients' electrolyte status.

Additionally, the article also provides precise insights into how patient characteristics and drug regimen can influence the extent of QTc prolongation, thereby offering a more tailored understanding of the associated risks. It highlights practical and clinical recommendations for managing electrolyte levels and adjusting drug dosages to optimize patient safety, which may not have been explicitly detailed in the past literature^{8,9}. By focusing on both pharmacological interactions and underlying patient factors, this review offers a more delicate approach to mitigate the cardiac risks in MDR-TB therapy, filling the notable gap in existing research.

METHODOLOGY

An extensive literature survey was conducted in PubMed, Scopus, ScienceDirect, and Google Scholar databases for studies published between 1988 and 2025. The inclusion criteria involved original and review articles evaluating the QT interval prolongation associated with bedaquiline, clofazimine, and fluoroquinolones in the treatment of drug-resistant tuberculosis. Articles without the data on QT prolongation, bedaquiline, clofazimine and fluoroquinolones, and MDR-TB were excluded.

Inclusion criteria

Original articles, review articles, clinical trials, regulatory and policy documents including WHO treatment guidelines and FDA prescribing information, related to the use of bedaquiline, clofazimine, and fluoroquinolones in MDR-TB and QT prolongation, which are published in English, are included in this review.

Exclusion criteria

The research articles that are not published in English and do not fit into the inclusion criteria are excluded. The original articles and review articles that don't contain relevant information are excluded. Articles for which the full text could not be retrieved were also excluded from the review.

Search strategy

The broad search method was employed to retrieve literature across all the databases mentioned. Bedaquiline, clofazimine, fluoroquinolones, MDR-TB, and QT prolongation were used as the population, and the search was conducted in the databases mentioned above.

Source of evidence selection

All the results from the databases were uploaded to Rayyan software, and duplicate articles from the databases were removed. The selection process was performed by two independent reviewers (DS and AK) in a blinded process, implementing a two-stage screening approach that involved first evaluating titles and abstracts, followed by a full-text assessment. The conflicts in the screening were resolved with the help

of a subject expert (KGS), and the articles were finalised for manuscript drafting.

Data extraction

The data extraction was performed by (MHK) in Microsoft Excel spreadsheets, and it was validated by (DS, AK & KGS). The data extraction was performed with the headings such as article title, journal name, name of authors, country, aspect of the study, drugs used, adverse events associated with QT prolongation, dosage if applicable, results, key findings and additional information.

CARDIAC ELECTROPHYSIOLOGY AND DRUG-INDUCED QTc PROLONGATION

Normal Ventricular Repolarization and the QTc Interval

The QT interval measured from the surface electrocardiogram (ECG) corresponds to the time needed for ventricular depolarization and repolarization. The process consists of the action potential (AP) of the ventricular myocyte, which goes through five phases from 0 to 4. Phase 3, corresponding to the rapid repolarization phase, is mostly conducted by potassium outflows such as rapid delayed rectifier potassium current (IKr) and slow delayed rectifier potassium current (IKs)¹⁰. The IKr channel is encoded by the hERG gene (KCNH2) and produces the hERG channel, which is sensitive to pharmacologic blockage because of the structure of its cavity for drug interactions, including aromatic amino acids interacting with various lipophilic drugs¹¹.

With respect to rate dependency, the QT interval needs to be corrected for heart rate. Bazett's correction is commonly used in the clinic ($QTc = QT/\sqrt{RR}$), whereas Fridericia's correction is believed to provide more accurate results in the case of an extreme heart rate ($QTc = QT/RR^{0.33}$)¹². The normal QTc range in men is less than 450 ms, whereas in women it is below 460 ms. When the QTc exceeds 500 ms, it is considered clinically significant concerning arrhythmia risk and usually requires medication adjustment according to guidelines^{5,13}.

Drug-Induced QTc Prolongation: Mechanism of hERG Channel Blockade

Drug-mediated QTc prolongation is usually caused by hERG channel blockage, which leads to a reduced IKr current and delay of phase 3 repolarization. Therefore, there is a prolonged AP duration, seen on an ECG as QTc prolongation¹¹. The hERG channel demonstrates increased sensitivity to drugs because of its wide and hydrophobic cavity as well as two aromatic amino acid residues (Tyr652 and Phe656) that act as binding sites for various drugs, including antihistamines, antipsychotics, antimalarials, and particularly anti-tuberculosis agents¹⁴.

If IKr is strongly inhibited either due to pharmacological effects or through genetic mutations, electrolyte disorders, etc., there is a depletion of repolarization reserves. The term "repolarization reserve" refers to the extra repolarizing mechanisms present in cells that normally protect against arrhythmias despite any disturbances in repolarization kinetics¹⁵. In the case of depletion of the repolarization reserve due to multiple factors (drug interactions with electrolyte imbalance), conditions promoting EADs and, consequently, Torsades de Pointes arise. Reactivation of the L-type calcium channel current occurs during the late part of the plateau phase of AP and results in EADs and arrhythmias¹⁶.

Electrolytes and Cardiac Repolarization

Potassium and magnesium are the two electrolytes that are essential for the stability of cardiac repolarization. They operate differently but are interlinked from a clinical perspective. Hypokalemia reduces the

concentration gradient for potassium flux through the hERG channel; however, owing to the requirement of extracellular potassium for the return of hERG channels from the inactivated state, it reduces IKr even though the gradient becomes more pronounced. Inward rectification occurs because fewer channels return from the inactivated state when potassium concentrations decrease in the blood¹⁷. Hence, similar to the blocking of hERG channels by antiarrhythmic drugs, hypokalemia results in a reduction in IKr and a prolonged duration of the AP and QTc interval. Clinical evidence suggests that hypokalemia is independently associated with QTc prolongation. In an emergency department cohort, Marill et al. reported that for serum potassium concentrations below 3.9 mmol/L, each 1 mmol/L decrease in potassium was associated with an increase in QTc of approximately 43 ms in women and 29.5 ms in men¹⁸.

Magnesium operates in two ways. First, it is a co-factor of Na⁺/K⁺-ATPase, and hypomagnesemia causes secondary potassium wasting. This means that the correction of hypokalemia may be difficult unless magnesium is replaced first¹⁹. Second, magnesium acts directly to stabilize the membrane voltage and inhibits the depolarizing current during prolonged APs. The absence of magnesium in hypomagnesemia increases the likelihood of EADs. TdP can only be treated using intravenous magnesium sulfate because of this duality²⁰.

This means that a prolonged QT interval induced by drug interaction and a prolonged QT interval due to electrolyte disturbance do not function independently of each other but are caused by a common mechanism. In patients who develop hypokalemia because of drug-induced hERG channel blockage, it does not just result in the addition of a constant value in the QT interval; instead, it causes a disproportionate increase in arrhythmogenicity¹⁵.

INDIVIDUAL DRUG PROFILES: QTc EFFECTS

Bedaquiline

Bedaquiline (BDQ) is a diarylquinoline antibiotic that acts on the Fo subunit of ATP synthase in mycobacteria, blocking energy generation²¹. It received approval from the FDA in 2012 as a result of accelerated approval, indicating its status as the first novel TB drug with a novel mechanism of action over four decades. Cardiac side effects are among the main challenges associated with the clinical development of bedaquiline.

BDQ is known to prolong the QT interval, at least in part through inhibition of the cardiac hERG channel, with dose- and concentration-dependent effect observed. In the Phase IIb randomized controlled pilot trial involving 47 patients with MDR-TB, the mean QTc increase at 24 weeks was 15.4 ms in the bedaquiline arm compared with 3.3 ms in the placebo group. Separately, 22.5% of patients receiving bedaquiline had QTc between 450–500 ms compared with 6.7% of placebo patients across the first two studies². However, this effect continues well beyond the 24-week period of bedaquiline administration because of an unusually long elimination half-life of approximately 5–6 months. The active metabolite M2, which tends to accumulate over time, has shown hERG-blocking properties, which contributes to the prolongation of QTc well after BDQ has been discontinued²².

In the Nix-TB trial, which evaluated the effectiveness of BDQ + pretomanid + linezolid (BPaL regimen) in treating Extensively Drug-Resistant Tuberculosis (XDR-TB), the maximum mean value of QTc was increased to 10 ms at week 16 of therapy²³. Importantly, no QTc prolongation was observed in the group taking linezolid as a part of the regimen; thus, all QTc prolongations were attributed solely to BDQ or BDQ with pre-existing risk factors. In the ZeNix trial, which assessed different linezolid doses in BPaL regimen, adverse events were comparable with those seen previously, providing more support to the above hypothesis²⁴.

The FDA prescribing information for bedaquiline includes a boxed warning for QT prolongation and cautions that concomitant use with other QT-prolonging drugs, including clofazimine, may result in additive QT prolongation. Consequently, ECG monitoring is recommended when these agents are used together²⁵.

Clofazimine

Clofazimine (CFZ) is an antiseptic riminophenazine agent with antimycobacterial and anti-inflammatory actions. Mechanisms underlying its effect include mycobacterial phospholipase A2 inhibition, electron transport interference, and production of reactive oxygen species²⁶. While historically used for leprosy treatment, CFZ was later adopted for use in multidrug-resistant tuberculosis (MDR-TB) treatment and became an integral component of the shortened WHO-recommended MDR-TB regimen (4-6 months BDQ-Cf-Lfx-Cs-Z/5 Lfx-Cf-Cs-Z).

QT interval (QTc) prolongation through concentration-dependent inhibition of the hERG channel represents the primary mechanism of CFZ. QTc prolongation in clinical trials for MDR-TB was reported to be about 16-20 ms on average in standard doses of clofazimine²⁷. CFZ shows unique pharmacokinetic characteristics, including high tissue accumulation within macrophages, fat, and the digestive tract and a very long terminal half-life (approximately 70 days), resulting in a persistent QTc effect beyond the period of dose decrease or discontinuation²⁶.

The additive effect of combining multiple QT-prolonging antituberculosis drugs has been demonstrated in pharmacokinetic-pharmacodynamic analyses. An exposure-QTc modeling study evaluating bedaquiline, pretomanid, and clofazimine estimated a maximum drug-induced QTc prolongation of approximately 44.5 ms when the three agents were coadministered. Although this increase was greater than that observed with individual drugs, clinically significant QT prolongation remained uncommon with appropriate monitoring²⁸. Therefore, this trial provides perhaps the best example of additive QTc effect in this drug combination.

It should be noted that QTc prolongation effect of clofazimine appears to be increased under conditions of hypokalemia. In retrospectively studied MDR-TB patients, 15% of the patients with serum potassium less than 3.5 mEq/L who received a CFZ regimen showed a markedly increased mean QTc when compared with those who received the same regimen with normal levels²⁹.

Fluoroquinolones

The mechanism of antimicrobial action of fluoroquinolones is associated with the blockage of DNA gyrase (topoisomerase II) and topoisomerase IV, leading to prevention of DNA supercoiling and repair³⁰. Regarding the QTc effect, fluoroquinolones as a drug class are known to cause QTc prolongation, but with significant inter-agent differences. The mechanism of QTc prolongation includes direct blockage of hERG channels (IKr) and, for some agents, additional blockage of the slow delayed rectifier potassium current (IKs). The combination of IKr and IKs blockages is more effective for repolarization reserve decrease compared to only IKr inhibition³¹.

In the context of MDR-TB, moxifloxacin is the most dangerous for the cardiac system and is clinically significant among fluoroquinolones. This agent has the highest impact on the QTc interval; a mean QTc prolongation of approximately 16.34–17.83 ms has been reported in TQT studies³². The choice of moxifloxacin as an MDR-TB drug is based on higher antimycobacterial efficacy than that of other fluoroquinolones, although this advantage should be considered in terms of increased cardiac risk when this drug is used, especially when it is combined with bedaquiline and clofazimine.

On the contrary, levofloxacin causes a weaker QTc prolongation effect (~6–8 ms); thus, it may be preferable under borderline QTc conditions³³. It is advisable in patients with progressive QT prolongation approaching clinically significant thresholds, substitution of moxifloxacin with levofloxacin may be considered after individualized assessment.

ADDITIVE QTc PROLONGATION WITH CONCURRENT BDQ, CFZ, AND FLUOROQUINOLONE USE

Pharmacological Basis of Additivity

When multiple drugs with separate QTc-prolonging mechanisms of action are used simultaneously, one expects their repolarization effects to be additive in many cases and even synergistic in others. Additivity occurs in cases where each drug acts by blocking hERG channels, although the magnitude of QT prolongation may vary depending on pharmacokinetic interactions and individual repolarization reserve³⁴. Such expectations are likely to apply to bedaquiline, clofazimine, and moxifloxacin, which utilize different mechanisms of action with regard to the binding site on the hERG protein.

BDQ, clofazimine, and moxifloxacin are associated with QT interval prolongation, and their concomitant use may increase the risk of additive QTc prolongation, particularly in the presence of electrolyte abnormalities⁹. Patients with a baseline QTc near the upper limit of normal may approach clinically significant QTc values when exposed to multiple QT-prolonging drugs, particularly in the presence of additional risk factors.

It should be emphasized that additive effects can actually understate the risk of arrhythmias since the repolarization reserve is not a linear phenomenon. When the QTc increases, the remaining repolarization reserve becomes lower in a non-linear manner, and the risk of TdP for each extra millisecond of prolongation increases¹⁵.

Clinical Evidence from Major MDR-TB Trials

Number of clinical trials have produced significant amounts of information related to QTc changes associated with bedaquiline-containing regimens (Table 1), although no studies have been specifically performed to assess the combined effects of these three drugs on QTc in a controlled way.

In the Standardized Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis (STREAM) Stage 2 trial, bedaquiline-containing regimens that also included clofazimine and a fluoroquinolone were associated with QTc prolongation;

however, QTcF ≥500 ms occurred in only a small proportion (3–6%) of participants, highlighting the need for regular ECG monitoring³⁵.

The Pragmatic Clinical Trial for a more Effective, Concise and Less Toxic Regimen (TB-PRACTECAL) trial compared three 24-week all-oral regimens BPAL, BPALC, and BPALM against standard-of-care therapy for rifampicin-resistant tuberculosis, provides some of the strongest clinical evidence currently available of QTc behaviour across multiple QTc-prolonging drug combinations; post-hoc ECG analysis revealed that the clofazimine-containing arm (BPALC) produced the highest mean peak QTcF of 446.5 ms, and across all three investigational arms, clinically significant QTc prolongation was rare under intensive monitoring conditions, with only one instance of QTcF >500 ms recorded among 3,744 ECG measurements^{36,37}.

The evaluation of fluoroquinolone therapy compared several regimens with variable use of fluoroquinolones. Comparisons revealed that, compared to levofloxacin, moxifloxacin generally demonstrated greater QT prolongation, consistent with the known pharmacological properties of these fluoroquinolones, directly demonstrating the additional QTc effect of the drug³⁸.

Data obtained through the FDA Adverse Event Reporting System (FAERS) revealed that patients taking bedaquiline-containing regimens may experience QTc-related events like TdP and sudden cardiac death. Despite being relatively rare (small number compared to the total number of patients), there were cases of TdP reported from real-world use (programs)³⁹.

Drug–Drug Pharmacokinetic Interactions

In addition to having pharmacodynamic additive effects, pharmacokinetic drug–drug interactions between these medicines can cause even greater exposure and QTc prolongation. While bedaquiline is metabolized mainly via the CYP3A4 pathway, the concomitant use of a strong CYP3A4 inhibitor increases the blood level of bedaquiline and increases its QTc effect⁴⁰. Despite clofazimine being a nonsubstrate for CYP enzymes, it can weakly inhibit CYP3A4 in the gut, causing increased exposure to bedaquiline.

In the case of MDR-TB in Human Immunodeficiency Virus (HIV) coinfecting patients on antiretroviral therapy, the extent of drug interaction increases. In such circumstances, lopinavir/ritonavir, widely used in resource-limited settings, is a strong inhibitor of CYP3A4 and is known to increase the plasma Area under the curve (AUC) of bedaquiline, consequently amplifying the effect on the QTc interval⁴¹. Although now described as requiring careful consideration

Table 1. Summary of major clinical trials evaluating the QTc prolongation outcomes in MDR-TB treatment regimen

Trial	Design	N	Regimen(s)	QTc Outcome	Key Conclusion
STREAM Stage 2 ³⁵	Open-label, multicentre, randomised, non-inferiority	1436	Bedaquiline + clofazimine + fluoroquinolone-containing regimens vs standard-of-care	QTcF ≥500 ms in 3–6% of participants	Regular ECG monitoring warranted; clinically severe QTc prolongation uncommon
TB-PRACTECAL ^{36,37}	Open-label, randomised, controlled, phase 2-3, multi-arm, non-inferiority	439	BPAL, BPALC, BPALM vs standard-of-care (all rifampicin-resistant TB)	Highest mean peak QTcF 446.5 ms in clofazimine-containing arm (BPALC); only 1 QTcF >500 ms recorded overall	Clinically significant QTc prolongation rare under intensive monitoring, even with 3-drug combinations
Nix-TB ²³	Open-label, single-arm trial	109	Bedaquiline + pretomanid + linezolid (BPAL) for XDR-TB	Maximum mean QTc increase ~10 ms; no prolongation attributed to linezolid	QTc effect attributable to bedaquiline component of BPAL, not linezolid
ZeNix ²⁴	Randomised, dose-finding trial	181	BPAL with varying linezolid doses	Cardiac adverse events comparable across linezolid-dose arms	Supports attribution of QTc effect to bedaquiline/pretomanid rather than linezolid

and monitoring, a programmatic combination of both medicines still occurs among MDR-TB and HIV-coinfected patients.

HYPOKALEMIA AND HYPOMAGNESEMIA AS MODIFIERS OF RISK FACTORS

Prevalence of Electrolyte Disturbances in MDR-TB

The electrolyte imbalances noted in MDR-TB patients are not coincidental; rather, they are the predictable outcome of both the pathophysiology and therapy of the disease. Malnutrition is common among patients with MDR-TB, particularly at treatment initiation; most of the patients with MDR-TB suffer from moderate to severe malnutrition at the beginning of the therapy⁶. This condition leads to a decrease in the body stores of potassium and magnesium intake, thus creating the basis for electrolyte deficiency even before the effect of the drugs come into play.

Companion drugs in MDR-TB regimens contribute substantially to electrolyte losses, as both ethionamide and prothionamide frequently cause nausea and vomiting leading to gastrointestinal losses of potassium and magnesium⁴². The new drug in preferred MDR-TB regimens, linezolid, leads to nausea, diarrhea, and decreases appetite in a significant number of patients. Furthermore, clofazimine may lead to gastrointestinal complications by itself, inducing abdominal pain and diarrhea in most patients²⁶.

In a retrospective case series of MDR-TB patients in Lima, Peru, hypokalemia (serum $K^+ < 3.5$ mEq/L) was detected in 31.3% of patients, with hypokalemia and hypomagnesemia identified as important adverse reactions of MDR-TB therapy, particularly among patients receiving capreomycin, highlighting the clinical importance of electrolyte monitoring in this population⁶.

Electrophysiological Mechanism of Hypokalemia-Driven QTc Prolongation

The electrophysiology of how hypokalemia contributes to QTc prolongation is straightforward yet paradoxical. One might expect that lowering the concentration of extracellular potassium should increase the outward potassium gradient and hasten repolarization, but this is not what happens¹⁷.

The hERG channel undergoes C-type inactivation, whereby the channel quickly enters an inactivated state after it opens. To come out of the inactivated state which is essential to generate outward current the channel needs a particular extracellular potassium to occupy a binding site in its outer vestibulum. With a low level of extracellular potassium, the binding site is under-filled, the channel cannot come out of inactivated state, remaining non-conductive¹⁷. Thus, a functional decrease in IKr occurs despite having an unblocked and intact channel and a fully parallel mechanism to drug hERG block.

Studies measuring the effects of varying levels of hypokalemia on QTc have obvious ethical restrictions since deliberate induction of an electrolyte imbalance is not feasible⁴³. Yet available evidence confirms the relationship between them. Osadchii et al. showed in their study with experimental heart preparation that IKr declined as the extracellular potassium was lowered from 4.0 to 2.0 mEq/L in a nearly linear manner¹⁷.

Hypomagnesemia: Primary Effects and Secondary Potassium Depletion

Magnesium acts as a cofactor in more than 300 enzymatic processes, among which is Na^+/K^+ -ATPase, an enzyme crucial for maintaining the intracellular concentration of potassium. The deficiency of magnesium adversely affects Na^+/K^+ -ATPase activity, leading to

increased potassium loss through urine and decreased effectiveness of oral potassium intake¹⁹.

This relationship is clinically significant since cases of hypokalemia resistant to supplementation in the absence of previously corrected hypomagnesemia have been reported. Patients with hypomagnesemia receiving intensive oral or intravenous potassium supplementation showed only temporary normalization of their serum potassium levels until further supplementation was stopped, due to persistent potassium loss through the urine⁴⁴. It should be noted that the administration of multiple agents causing loss of both potassium and magnesium might lead to the development of progressively resistant electrolyte imbalance in MDR-TB patients.

Magnesium also affects cardiac membranes in a direct way by blocking voltage-dependent sodium and calcium channels and decreasing the frequency of EAD formation, increasing the threshold of triggering mechanisms for TdP formation²⁰. Based on this knowledge, magnesium sulfate needs to be administered intravenously at the onset of TdP and used as a prophylactic administration TdP in patients receiving QTc-prolonging agents.

Quantifying the Combined Drug and Electrolyte QTc Risk

Pharmacologically derived conceptual framework for risk assessment of drugs in combination with electrolyte-induced prolongation of QTc relies on pharmacological effects of all involved agents together with their effects on electrolytes' concentrations⁴⁵.

In a patient with MDR-TB, a baseline QTc that is already near the upper normal range can become clinically concerning during treatment with bedaquiline, clofazimine, and fluoroquinolone, especially if hypokalemia or hypomagnesemia is present⁶. Rather than presenting a precise additive estimate, it is more defensible to state that this drug combination, together with uncorrected electrolyte abnormalities, can raise QTc into a range that approaches or exceeds 500 ms, which is consistent with observed MDR-TB cohorts. Correction of reversible factors, particularly potassium and magnesium deficits, is therefore important when interpreting QTc risk during MDR-TB therapy⁴⁶.

RISK STRATIFICATION, MONITORING, AND CLINICAL MANAGEMENT

Patient-level risk assessment

QTc risk stratification guidelines need to be applied systematically before starting any MDR-TB regimen incorporating two or more drugs with QTc-prolonging capability^{47,48}.

Clinical factors for QTc prolongation and development of TdP include female gender (women have an inherent 10–15 ms higher QTc compared to men do and are twice as likely to develop TdP caused by medications), aged over 60 years, cardiac disease (especially structural heart disease, heart failure, and bradycardia), congenital long QT syndrome, hepatic dysfunction, which decreases bedaquiline clearance, and the administration of other drugs that can prolong QTc^{13,49}.

Baseline 12-lead ECG should be done before starting bedaquiline or any other QTc-prolonging MDR-TB medication. In patients with baseline QTc values exceeding 450 ms in men or 470 ms in women require careful evaluation, correction of reversible risk factors, and closer ECG monitoring before initiation of QT-prolonging therapy³. Baseline electrolyte panels, including potassium, magnesium, and calcium, should also be performed simultaneously with the ECG, and the correction of identified abnormalities, if present, ideally would be done before treatment initiation.

WHO and International Programme Guidance on QTc Monitoring

The WHO consolidated guidelines for tuberculosis 2022 contain specific guidelines regarding QTc monitoring in patients receiving bedaquiline. Electrocardiography monitoring should be performed prior to treatment; at weeks 2, 4, 8, and 12 during the intensive phase; and then monthly after that period³. Monitoring of electrolytes should be done similarly, although in resource-limited settings, implementation may be challenging⁶.

Electrolyte Monitoring and Correction Protocol

Monitoring of electrolytes in MDR-TB patients on treatment should ideally be done at least once per month; more frequent monitoring may be considered when QTc approaches clinically significant thresholds or electrolyte abnormalities are detected. Serum potassium and serum magnesium are the most important electrolytes to be monitored since magnesium plays a critical role in the functioning of Na⁺/K⁺-ATPase pumps. Also, monitoring of serum calcium is important since QTc is prolonged in patients with calcium imbalances and it is associated with hypomagnesemia¹⁹.

The target electrolyte values for correcting electrolyte imbalances in QTc-prolonging MDR-TB drugs should aim at higher concentrations than the normal clinical lower limits^{50,51}.

For serum potassium, a target of ≥ 4.0 mEq/L is advised (as compared to the normal lower limit of 3.5 mEq/L). This is because the potassium value offers enough repolarization reserve when it is near normal. Maintaining serum magnesium within the normal range (preferably around or above 0.85 mmol/L in high-risk patients) is recommended as the serum magnesium to provide adequate function of Na⁺/K⁺-ATPase enzymes and reduce the potassium loss caused by hypomagnesemia.

One important principle is that of magnesium first. Hypokalemia must not be addressed solely using potassium. This is because in the absence of magnesium, potassium will be quickly eliminated by the kidneys; hence, no benefit is realized⁴⁴. Where intravenous administration of magnesium is not possible due to resource limitations, oral administration using magnesium glycinate or magnesium oxide serves the purpose well if a patient does not have severe magnesium deficiency.

Drug Modification Strategies for Elevated QTc

When QTc reaches or exceeds established critical thresholds, a hierarchical approach for the drug modification can be applied. The modification will be based on balancing between QTc risk and the microbiologic/clinical importance of the drug in the regimen⁸.

The first modification step is a substitution of moxifloxacin by levofloxacin, which decreases the effect of fluoroquinolone on QTc by about 6-8 ms but still preserves its antimicrobial activity despite lower activity in multidrug-resistant strains of *Mycobacterium tuberculosis*^{33,52}. Substitution can be considered in patients with progressive QT prolongation after correction of reversible causes.

If QTc is elevated further despite switching to another fluoroquinolone and aggressive correction of electrolytes, then one must reconsider its administration⁵³. It is better to avoid stopping this drug, as it plays a crucial role in contemporary MDR-TB regimens. If it is impossible, alternative regimens should be individualized according to WHO recommendations and drug susceptibility results.

Delamanid, a nitro-dihydro-imidazooxazole with high antimicrobial activity, causes an elevation of QTc by about 8.6 ms through inhibition of both IKr and IKs currents⁵⁴. Delamanid alone cannot serve as a safe alternative for bedaquiline in the cases of increased QTc but might be incorporated into individualized regimens when clinically appropriate.

Its use together with bedaquiline requires a strict evaluation of benefits vs risks.

SPECIAL POPULATIONS

HIV Coinfected Patient

HIV-positive patients are at the greatest risk of drug-induced QTc prolongation due to the high baseline prevalence of malnutrition, a higher risk of developing electrolyte abnormalities due to the effects of antiretroviral medication and HIV enteropathy, and the presence of several other agents which are known to prolong the QTc interval within the antiretroviral regimen⁴¹. The most clinically significant drug interaction with the bedaquiline regimen is with lopinavir/ritonavir. This combination results in an increase in the AUC of the bedaquiline drug profile by approximately 22%, leading to an elevated level of the drug in circulation and subsequently to QTc prolongation⁴⁰. The combination of these drugs should be avoided if possible, and substitution of the antiretroviral regimen is preferred if possible, with preference given to a regimen that includes dolutegravir, which does not inhibit CYP3A4 or prolong the QTc interval itself.

A prospective study evaluating bedaquiline-related QTc prolongation in patients with multidrug-resistant tuberculosis (MDR-TB) reported that 11.3% of patients developed mild QTc prolongation, 3.8% experienced moderate prolongation, and 1.9% developed severe QTc prolongation during treatment. Temporary withdrawal of bedaquiline (BDQ) was required in 1.96% of patients during the first 3 months of therapy because of severe QTc prolongation. By the 6-month follow-up, QTc abnormalities had improved considerably, with no patients exhibiting severe QTc prolongation and only 1.9% continuing to have moderate QTc prolongation. These findings support the overall cardiac safety profile of BDQ when used with appropriate monitoring and reaffirm its central role in the treatment of multidrug-resistant tuberculosis. They also underscore the importance of regular electrocardiographic (ECG) and QTc monitoring, particularly during the first 3 months of therapy, when the risk of clinically significant QTc prolongation is highest⁵⁵.

Diabetic and Elderly Patients

Patients with autonomic neuropathy in diabetes mellitus (DM) are prone to impaired cardiac rate adaptation and QTc prolongation and are hence vulnerable to a greater risk of developing QTc prolongation induced by medications⁵⁶. In addition, antihypertensive diuretics such as thiazide and loop diuretics, which are often used in diabetic patients, contribute to potassium and magnesium wasting and establish or exacerbate electrolyte deficiencies in MDR-TB therapy. Elderly patients (aged > 60 years) have a higher absolute risk of TdP associated with the use of medications that induce QTc prolongation owing to a decreased capacity to handle electrolyte disturbances, increased polypharmacy, and advanced age.

A review by Maranchick et al. on the role of therapeutic drug monitoring (TDM) in the treatment of multidrug-resistant tuberculosis (MDR-TB) highlights that DM impairs the host immune response to *Mycobacterium tuberculosis*, resulting in more rapid disease progression and a higher mycobacterial burden. It also notes that altered pharmacokinetics in patients with DM, together with adverse effects of anti-tuberculosis drugs that may overlap with the progression of DM, can complicate treatment. Furthermore, evidence summarized in the review indicates that patients with DM are more likely to exhibit delayed treatment responses and subtherapeutic anti-TB drug concentrations, supporting the potential utility of TDM in this population. By incorporating TDM into clinical practice, clinicians can distinguish adverse effects related to drug overexposure from those associated with disease progression and optimize dosing to improve treatment efficacy while minimizing toxicity⁵⁷.

Paediatric MDR-TB

In May 2020, the US FDA expanded the approval of bedaquiline to include children aged ≥ 5 years and weighing at least 15 kg with pulmonary MDR-TB. Subsequently, the WHO initially recommended bedaquiline for children aged 6–17 years (2020 guidance), and later, in its 2022 consolidated guidelines, conditionally recommended its use in children of all ages, including those younger than 6 years, as part of an all-oral regimen for MDR/RR-TB⁵⁸. QTc levels vary with age in pediatrics; thus, age-appropriate reference values must be used when interpreting QTc levels in this group. Electrolyte disturbances may be accentuated in this group because of the high incidence of enteric pathology and the higher metabolic demands related to growing.

A Phase II, open-label, multicenter, single-arm study evaluating bedaquiline in 30 pediatric patients with multidrug-resistant tuberculosis (MDR-TB)⁵⁹ demonstrated that the drug was generally well tolerated. The 24-week safety analysis identified arthralgia, nausea, abdominal pain, QTc prolongation, and hepatotoxicity as the most reported adverse events, with children exhibiting a more favorable safety profile than that typically observed in adults⁶⁰.

Risk Prediction

Current prediction models therefore have important limitations, as they rely predominantly on baseline demographic and treatment-related variables and do not account for dynamic biochemical changes that occur during therapy^{61–64}.

Accumulating evidence indicates that hypokalemia and hypomagnesemia are major modifiable contributors to drug-induced QTc prolongation by impairing myocardial repolarization and increasing susceptibility to ventricular arrhythmia, particularly in patients receiving multiple QT-prolonging agents^{65–67}.

Population pharmacokinetic-pharmacodynamic analyses of bedaquiline have further demonstrated that lower serum potassium and calcium concentrations are associated with longer QTc intervals, supporting the biological relevance of electrolyte status in determining QT risk^{68–70}.

Some programs have adopted a QTc prediction tool for patients receiving bedaquiline, and the published nomogram is derived from baseline QTc, creatinine, sex, resistance status, and coadministration of fluoroquinolones or clofazimine and does not include electrolyte parameters⁷¹. The inclusion of baseline QTc values, serum potassium levels, serum magnesium levels, sex, and other risk factors for QTc prolongation in a score will allow the development of a practical decision support tool.

A clinical scoring system has been derived using the RISQ-PATH study, which uses patient factors, concomitant diseases, QT-prolonging drugs taken by patients, and biochemical factors for QTc prolongation due to medications⁷². Although this study does not directly focus on MDR-TB patients, it emphasizes the need for inclusion of electrolyte factors in such a risk prediction model.

A relatively new method of risk stratification is the use of biomarkers to move past the current use of strict clinical and demographic parameters in predicting risk⁷³. This research study has managed to identify specific urine biomarkers that have been found to predict prolonged QTc intervals in MDR-TB patients undergoing treatment using bedaquiline. In essence, this represents a biological risk stratification approach that serves as an alternative to the current models based only on clinical and demographic parameters; however, this method is still at a preliminary stage and requires external validation before it can be utilized practically in limited resource settings for MDR-TB patients.

Future studies for risk prediction in MDR-TB patients must include repeated measurements of potassium and magnesium levels in serum. QTc prediction tools should integrate both static and dynamic risk factors, including serial serum potassium and magnesium concentrations, baseline QTc interval, renal function, sex, age, comorbidities, and concomitant QT-prolonging medications. Such approach could improve predictive accuracy, enable real-time risk stratification, facilitate timely electrolyte correction and medication adjustment, and ultimately reduce treatment interruptions while improving the cardiac safety of bedaquiline-containing MDR-TB regimens. Prospective multicenter studies are warranted to validate electrolyte-integrated prediction models before their implementation in routine clinical practice.

DISCUSSION AND CONCLUSION

Theoretical mechanisms suggest that imbalances in key electrolytes, notably potassium and magnesium, can significantly affect cardiac repolarization processes⁷⁴. For example, reductions in potassium levels can prolong the cardiac action potential, thereby potentially increasing the risk of QTc prolongation⁷⁵. However, these associations primarily stem from laboratory studies and require clinical validation.

Several observational studies have reported a correlation between electrolyte disturbances and QTc prolongation in various populations, including those undergoing treatment for MDR-TB⁶. While these findings underscore the association, it is essential to note that they often involve confounding factors, such as the effects of co-administered medications, that may also influence QTc dynamics⁷⁶. Therefore, while there is supporting evidence, the strength of these observational studies varies, and conclusions should be drawn with caution.

Currently, there is limited direct clinical evidence linking electrolyte disturbances specifically to adverse clinical outcomes, such as torsades de pointes, in patients being treated for MDR-TB. Few randomized controlled trials have been conducted to establish a definitive causal relationship^{77,78}. This absence of robust clinical data implies that while the theoretical risk exists, it has not yet translated into clearly defined clinical outcomes in this specific patient population.

Based on available expert opinions and research evidence, three crucial clinical takeaways can be outlined. The first is the inclusion of regular electrolyte screening as an integral part of the QTc monitoring routine among MDR-TB patients, at least once per month or more frequently if the patient's QTc values approach the danger zone. In such cases, the recommended electrolyte correction strategy is to maintain potassium ≥ 4.0 mEq/L⁷⁹ and correct magnesium deficiency (preferably to > 0.85 mmol/L in high-risk patients), which may reduce QT-related risk. Moreover, the second goal is to follow the magnesium-first rule since potassium replenishment would not help without addressing concurrent hypomagnesemia¹⁹. Finally, the third recommendation is to switch to levofloxacin when the patient's QTc approaches 480 ms; this intervention is associated with a reduction in QTc prolongation of 6–8 ms in most cases^{3,33}.

Overall, while electrolyte disturbances theoretically contribute to QTc prolongation and warrant clinical attention, the evidence supporting this relationship remains primarily observational and mechanistic. Given the complexity of managing patients with evolving electrolyte levels, particularly in those with additional risk factors such as HIV infection or DM, a cautious approach is to monitor and manage these levels closely in clinical practice. Future research is warranted to establish the real-time impact of electrolyte management on QTc prolongation, specifically through well-designed clinical trials to clarify these associations. The clinicians should maintain vigilance for QTc prolongation, recognizing that while risks are present, the current

evidence base does not fully substantiate them with proven clinical outcomes. Further research will help elucidate these relationships and guide more definitive recommendations.

Future Directions

There are no prospective clinical trials that have been conducted to determine whether the additive effect of bedaquiline-clofazimine-fluoroquinolone on the increase in QTc is dependent on baseline and evolving electrolyte levels. Furthermore, the role of pharmacogenomics in QTc assessment in MDR-TB needs to be explored. Known genetic variants in the KCNH2 (hERG) and KCNQ1 (KvLQT1) genes and their downstream pathways have been linked to increased sensitivity to QTc-prolonging medications in the general population needs to be studied¹¹.

Optimal electrolyte supplementation regimen for MDR-TB patients on QTc-prolonging therapy remains untested in a randomized controlled trial. Current recommendations regarding electrolyte target in the MDR-TB population with QTc prolongation are based on extrapolation of general cardiovascular practices¹⁹. Randomized controlled trials with comparisons of standard treatment against intensive protocol-based electrolyte supplementation targeting K⁺ and Mg²⁺ concentrations will help clarify whether this approach improves cardiac safety among MDR-TB patients.

ACKNOWLEDGEMENTS

We thank the Manipal College of Pharmaceutical Sciences and Manipal Academy of Higher Education for providing premium platforms such as Rubriq, Grammarly, and Turnitin for language editing and plagiarism checks.

REFERENCES

- Kasaeva Tereza, Ghebreyesus Tedros. Global report tuberculosis 2025. WHO. November 12, 2025. Accessed June 25, 2026. <https://www.who.int/publications/i/item/9789240116924>
- Diacon AH, Pym A, Grobusch MP, et al. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *New England Journal of Medicine*. 2014;371(8). doi:10.1056/nejmoa1313865
- World Health Organization. *WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2022 Update. : World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. 2022.*
- Guglielmetti L, Tiberi S, Burman M, et al. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: A Tuberculosis Network European Trialsgroup (TBnet) study. *European Respiratory Journal*. 2018;52(2). doi:10.1183/13993003.00537-2018
- Roden DM. Drug-Induced Prolongation of the QT Interval. *New England Journal of Medicine*. 2004;350(10). doi:10.1056/nejmra032426
- Shin S, Furin J, Alcántara F, et al. Hypokalemia among patients receiving treatment for multidrug-resistant tuberculosis. *Chest*. 2004;125(3). doi:10.1378/chest.125.3.974
- Babu LP, Babu J V, George S, Robin N, Jose J. Adverse Drug Reactions in Drug-Resistant Tuberculosis Management: A Clinical Approach. *Indian Journal of Pharmacy Practice*. 2021;14(2). doi:10.5530/ijopp.14.2.16
- Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: A systematic and critical analysis of the evidence. *European Respiratory Journal*. 2017;50(5). doi:10.1183/13993003.01462-2017
- Li R, Ma JB, Yang H, et al. Effects of Bedaquiline Combined with Fluoroquinolone and/or Clofazimine on QT Interval in Patients with Multidrug-Resistant Tuberculosis: a Retrospective Study. *Microbial Spectr*. 2023;11(4). doi:10.1128/spectrum.01048-23
- Locati ET, Bagliani G, Padeletti L. Normal Ventricular Repolarization and QT Interval: Ionic Background, Modifiers, and Measurements. *Card Electrophysiol Clin*. 2017;9(3). doi:10.1016/j.ccep.2017.05.007
- Thomas D, Karle C, Kiehn J. The Cardiac hERG/IKr Potassium Channel as Pharmacological Target: Structure, Function, Regulation, and Clinical Applications. *Curr Pharm Des*. 2006;12(18). doi:10.2174/138161206777585102
- Shah RR. The significance of QT interval in drug development. In: *British Journal of Clinical Pharmacology*. Vol 54. 2002. doi:10.1046/j.1365-2125.2002.01627.x
- Grouthier V, Moey MYY, Gandjbakhch E, et al. Sexual dimorphisms, anti-hormonal therapy and cardiac arrhythmias. *Int J Mol Sci*. 2021;22(3). doi:10.3390/ijms22031464
- Wang X, Liu J, Pan S, et al. BEDAQUILINE INDUCES THE UBIQUITINATION-DEPENDENT DEGRADATION OF MATURE HERG CHANNEL. *J Am Coll Cardiol*. 2023;81(8). doi:10.1016/s0735-1097(23)00503-x
- Roden DM. Editorial: Repolarization reserve: A moving target. *Circulation*. 2008;118(10). doi:10.1161/CIRCULATIONAHA.108.798918
- Lerman BB, Markowitz SM, Cheung JW, Thomas G, Ip JE. Ventricular Tachycardia Due to Triggered Activity: Role of Early and Delayed Afterdepolarizations. *JACC Clin Electrophysiol*. 2024;10(2). doi:10.1016/j.jacep.2023.10.033
- Osadchii OE. Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundam Clin Pharmacol*. 2010;24(5). doi:10.1111/j.1472-8206.2010.00835.x
- Marill KA, Miller ES. Hypokalemia in women and methadone therapy are the strongest non-cardiologic factors associated with QT prolongation in an emergency department setting. *J Electrocardiol*. 2017;50(4). doi:10.1016/j.jelectrocard.2017.02.001
- Whang R, Whang DD, Ryan MP. Refractory Potassium Repletion: A Consequence of Magnesium Deficiency. *Arch Intern Med*. 1992;152(1). doi:10.1001/archinte.1992.00400130066006
- Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. *Circulation*. 1988;77(2). doi:10.1161/01.CIR.77.2.392
- Preiss L, Langer JD, Yildiz Ö, et al. Structure of the mycobacterial ATP synthase Fo rotor ring in complex with the anti-TB drug bedaquiline. *Sci Adv*. 2015;1(4). doi:10.1126/sciadv.1500106
- Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *Journal of Antimicrobial Chemotherapy*. 2014;70(4). doi:10.1093/jac/dku504
- Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *New England Journal of Medicine*. 2020;382(10). doi:10.1056/nejmoa1901814
- Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. *New England Journal of Medicine*. 2022;387(9). doi:10.1056/nejmoa2119430
- fda, cder. HIGHLIGHTS OF PRESCRIBING INFORMATION. Accessed July 3, 2026. www.fda.gov/medwatch.
- Cholo MC, Steel HC, Fourie PB, Germishuizen WA, Anderson R. Clofazimine: Current status and future prospects. *Journal of Antimicrobial Chemotherapy*. 2012;67(2). doi:10.1093/jac/dkr444
- Abdelwahab MT, Court R, Everitt D, et al. Effect of clofazimine concentration on qt prolongation in patients treated for tuberculosis. *Antimicrob Agents Chemother*. 2021;65(7). doi:10.1128/AAC.02687-20
- Abdelwahab MT, Svensson E, Diacon A, et al. CONCENTRATION-QT MODELING of BEDAQUILINE, CLOFAZIMINE, and PRETOMANID in TB PATIENTS. *Top Antivir Med*. 2022;30(1 SUPPL).

29. Hughes G, Bern H, Chiang CY, et al. QT prolongation in the STREAM Stage 1 Trial. *International Journal of Tuberculosis and Lung Disease*. 2022;26(4). doi:10.5588/ijtld.21.0403
30. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiology and Molecular Biology Reviews*. 1997;61(3). doi:10.1128/mmbr.61.3.377-392.1997
31. Etchegoyen CV, Keller GA, Mrad S, Cheng S, Di Girolamo G. Drug-induced QT Interval Prolongation in the Intensive Care Unit. *Curr Clin Pharmacol*. 2018;12(4). doi:10.2174/1574884713666180223123947
32. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther*. 2003;73(4). doi:10.1016/S0009-9236(03)00009-2
33. Taubel J, Naseem A, Harada T, et al. Levofloxacin can be used effectively as a positive control in thorough QT/QTc studies in healthy volunteers. *Br J Clin Pharmacol*. 2010;69(4). doi:10.1111/j.1365-2125.2009.03595.x
34. Wiśniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect - comprehensive overview of clinical trials. *BMC Pharmacol Toxicol*. 2016;17(1). doi:10.1186/s40360-016-0053-1
35. Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *The Lancet*. 2022;400(10366). doi:10.1016/S0140-6736(22)02078-5
36. Motta I, Cusinato M, Ludman AJ, et al. How much should we still worry about QTc prolongation in rifampicin-resistant tuberculosis? ECG findings from TB-PRACTECAL clinical trial. *Antimicrob Agents Chemother*. 2024;68(7). doi:10.1128/aac.00536-24
37. Nyang'wa BT, Berry C, Kazounis E, et al. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med*. 2024;12(2):117-128. doi:10.1016/S2213-2600(23)00389-2
38. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *Int J Antimicrob Agents*. 2007;29(4). doi:10.1016/j.ijantimicag.2006.11.011
39. Wei S, He C, Xie X, et al. Which fluoroquinolone is safer when combined with bedaquiline for tuberculosis treatment: evidence from FDA Adverse Event Reporting System database from 2013 to 2024. *Front Pharmacol*. 2024;15. doi:10.3389/fphar.2024.1491921
40. Chahine EB, Karaoui LR, Mansour H. Bedaquiline: A Novel Diarylquinoline for Multidrug-Resistant Tuberculosis. *Annals of Pharmacotherapy*. 2014;48(1). doi:10.1177/1060028013504087
41. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58(11). doi:10.1128/AAC.03246-14
42. Shin SS, Pasechnikov AD, Gelmanova IY, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *International Journal of Tuberculosis and Lung Disease*. 2007;11(12).
43. Panduranga VT, John S, Sabu J, et al. 26-A-10400-ACC IMPACT OF SEVERITY OF HYPOKALEMIA ON CORRECTED QT INTERVAL PROLONGATION: A LARGE RETROSPECTIVE CROSS SECTIONAL STUDY FROM AN INNER-CITY HOSPITAL. *J Am Coll Cardiol*. 2026;87(13):A16. doi:10.1016/J.JACC.2026.02.041
44. ZS Agus. DISEASE OF THE MONTH, Hypomagnesemia. *Journal of the American Society of Nephrology*. 1999;10(7).
45. Ji Y, Johannesen L, Garnett C. FDA's insights: implementing new strategies for evaluating drug-induced QTc prolongation. *J Pharmacokinetic Pharmacodyn*. 2025;52(4). doi:10.1007/s10928-025-09985-4
46. Kusmiati T, Mertaniasih NM, Putranto JNE, et al. Factors that contribute to the QTc interval prolongation in DR-TB patients on STR regimen. *Indian Journal of Forensic Medicine and Toxicology*. 2021;15(1). doi:10.37506/ijfmt.v15i1.13641
47. Priori SG, Schwartz PJ, Napolitano C, et al. Risk Stratification in the Long-QT Syndrome. *New England Journal of Medicine*. 2003;348(19):1866-1874. doi:10.1056/NEJMOA022147;PAGE:STRING:ARTICLE/CHAPTER
48. Schwartz PJ, Crotti L. Long QT Syndrome. *New England Journal of Medicine*. 2025;393(20):2023-2034. doi:10.1056/NEJMRA2400853
49. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female Gender as a Risk Factor for Torsades de Pointes Associated With Cardiovascular Drugs. *JAMA: The Journal of the American Medical Association*. 1993;270(21). doi:10.1001/jama.1993.03510210076031
50. Amarh E, Overholser BR. Strategies for prevention and management of QT interval prolongation and torsades de pointes. *Torsades de Pointes*. Published online January 1, 2022:303-333. doi:10.1016/B978-0-12-821446-6.00011-0
51. Yadav S. Electrolyte disruption in drug-resistant tuberculosis: Managing risks for improved treatment outcomes. *IP Indian Journal of Immunology and Respiratory Medicine*. 2025;9(2):49-50. doi:10.18231/J.IJIRM.2024.010
52. Täubel J, Prasad K, Rosano G, et al. Effects of the Fluoroquinolones Moxifloxacin and Levofloxacin on the QT Subintervals: Sex Differences in Ventricular Repolarization. *J Clin Pharmacol*. 2020;60(3):400-408. doi:10.1002/JCPH.1534
53. Koele SE, Van Beek SW, Maartens G, Brust JCM, Svensson EM. Optimized Loading Dose Strategies for Bedaquiline When Restarting Interrupted Drug-Resistant Tuberculosis Treatment. *Antimicrob Agents Chemother*. 2022;66(3). doi:10.1128/aac.01749-21
54. Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infect Dis*. 2021;21(7). doi:10.1016/S1473-3099(20)30770-2
55. Gupta A, Pais CC, Babu S. Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study. *Journal of Association of Physicians of India*. 2026;74(2):91-93. doi:10.59556/JAPI.74.1361
56. Veglio M, Chinaglia A, Cavallo-Perin P. QT interval, cardiovascular risk factors and risk of death in diabetes. *J Endocrinol Invest*. 2004;27(2). doi:10.1007/BF03346265
57. Maranchick NF, Peloquin CA. Role of therapeutic drug monitoring in the treatment of multi-drug resistant tuberculosis. *J Clin Tuberc Other Mycobact Dis*. 2024;36:100444. doi:10.1016/J.JCTUBE.2024.100444
58. WHO consolidated guidelines on tuberculosis. Module 5, Management of tuberculosis in children and adolescents. Published online 2022:101.
59. Gaensbauer JT, Dash N, Verma S, et al. Multidrug-resistant tuberculosis in children: A practical update on epidemiology, diagnosis, treatment and prevention. *J Clin Tuberc Other Mycobact Dis*. 2024;36:100449. doi:10.1016/J.JCTUBE.2024.100449
60. Moodliar R, Aksenova V, Frias IV MVG, et al. Bedaquiline for multidrug-resistant TB in paediatric patients. *The International Journal of Tuberculosis and Lung Disease*. 2021;25(9):716. doi:10.5588/IJTL.21.0022
61. Jin Y, Kattan MW. Methodologic Issues Specific to Prediction Model Development and Evaluation. *Chest*. 2023;164(5):1281-1289. doi:10.1016/J.CHEST.2023.06.038
62. Saelmans A, Seinen T, Pera V, et al. Implementation and Updating of Clinical Prediction Models: A Systematic Review. *Mayo Clinic*

- Proceedings: Digital Health.* 2025;3(3):100228. doi:10.1016/J.MCPDIG.2025.100228
63. Zhao Q, Zhang C, Zhang W, Zhang S, Liu Q, Guo Y. Applications and challenges of biomarker-based predictive models in proactive health management. *Front Public Health.* 2025;13:1633487. doi:10.3389/FPUH.2025.1633487/FULL
 64. Calster B Van, Smeden M van, Amsterdam W van, Coemans M, Wynants L, Steyerberg EW. The Enemies of Reliable and Useful Clinical Prediction Models: A Review of Statistical and Scientific Challenges. *Annu Rev Stat Appl.* 2026;13(Volume 13, 2026):465-492. doi:10.1146/ANNUREV-STATISTICS-042324-123749
 65. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, Risk Factors, and Management of Acquired Long QT Syndrome: A Comprehensive Review. *The Scientific World Journal.* 2012;2012:212178. doi:10.1100/2012/212178
 66. TeBay C, Hill AP, Windley MJ. Metabolic and electrolyte abnormalities as risk factors in drug-induced long QT syndrome. *Biophysical Reviews* 2022 14:1. 2022;14(1):353-367. doi:10.1007/S12551-022-00929-7
 67. Cabahug MC, Vempati A. Torsade de Pointes Due to Hypokalemia and Hypomagnesemia. *Journal of Education & Teaching in Emergency Medicine.* 2022;7(4):S27. doi:10.21980/J8JP8G
 68. Li J, Yang G, Cai Q, et al. Safety, efficacy, and serum concentration monitoring of bedaquiline in Chinese patients with multidrug-resistant tuberculosis. *International Journal of Infectious Diseases.* 2021;110:179-186. doi:10.1016/J.IJID.2021.07.038
 69. Tanneau L, Karlsson MO, Rosenkranz SL, et al. Assessing Prolongation of the Corrected QT Interval with Bedaquiline and Delamanid Coadministration to Predict the Cardiac Safety of Simplified Dosing Regimens. *Clin Pharmacol Ther.* 2022;112(4):873. doi:10.1002/CPT.2685
 70. Lin YJ, Okibedi F, Karlsson MO, Svensson EM. An Interactive Pharmacokinetic-Pharmacodynamic Framework to Evaluate Bedaquiline Dose Modifications in Adults With Tuberculosis. *CPT Pharmacometrics Syst Pharmacol.* 2026;15(5):e70264. doi:10.1002/PSP4.70264;PAGEGROUP:STRING:PUBLICATION
 71. Liu F, Gao J, Gao M, et al. Development and Validation of a Nomogram for Prediction of QT Interval Prolongation in Patients Administered Bedaquiline-Containing Regimens in China: a Modeling Study. *Antimicrob Agents Chemother.* 2022;66(9). doi:10.1128/aac.02033-21
 72. Vandael E, Vandenberg B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. *International Journal of Clinical Pharmacy* 2017 39:2. 2017;39(2):424-432. doi:10.1007/S11096-017-0446-2
 73. Yu J, Ren W, Yuan J, et al. Identification of urine biomarkers predictive of prolonged QTc interval in multidrug-resistant tuberculosis patients treated with bedaquiline. *Front Pharmacol.* 2024;15:1362544. doi:10.3389/FPHAR.2024.1362544/TEXT
 74. Noordam R, Young WJ, Salman R, et al. Effects of Calcium, Magnesium, and Potassium Concentrations on Ventricular Repolarization in Unselected Individuals. *J Am Coll Cardiol.* 2019;73(24):3118. doi:10.1016/J.JACC.2019.03.519
 75. Weiss JN, Qu Z, Shivkumar K. The Electrophysiology of Hypo- and Hyperkalemia. *Circ Arrhythm Electrophysiol.* 2017;10(3):e004667. doi:10.1161/CIRCEP.116.004667
 76. Yuan N, Oesterle A, Botting P, et al. High-Throughput Assessment of Real-World Medication Effects on QT Interval Prolongation: Observational Study. *JMIR Cardio.* 2023;7:e41055. doi:10.2196/41055
 77. Anand AB, Malur K, Sabnis GR, Mahajan AU. A case series of drug-induced torsades de pointes in patients on multidrug-resistant tuberculosis treatment: Beware the gift that conceals a blade. *Heart Rhythm O2.* 2024;5(5):324. doi:10.1016/J.HROO.2024.03.007
 78. Bulloch MN, Cardinale-King M, Cogle · Sarah, et al. Correction of Electrolyte Abnormalities in Critically Ill Patients. *Intensive Care Research* 2024 4:1. 2024;4(1):19-37. doi:10.1007/S44231-023-00054-3
 79. Cohagan B, Brandis D. Torsade de Pointes. *StatPearls.* Published online August 8, 2023. Accessed July 26, 2026. <https://www.ncbi.nlm.nih.gov/books/NBK459388/>

Cite this article: Hariprasad K M, Disha S, Amruth K, Manjunath S, Arul A, Devasrita D, Tatiyana M, Ganesh S K. Additive QTc Prolongation with Concurrent Use of Bedaquiline, Clofazimine, and Fluoroquinolones in MDR-TB: Role of Hypokalemia and Hypomagnesemia as Modifying Risk Factors. *Pharmacogn J.* 2026;18 (3): 348-357.