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Review Article

Mexiletine in the treatment of LQT2, LQT3, and acquired LQTS: a meta-analysis

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Abstract

High mortality in patients with Long QT Syndrome (LQTS) can be reduced with proper treatment. Gene-specific therapy is crucial, as many treatments are not equally effective across different LQTS types. While mexiletine has been established in the treatment of LQT3, its use in other types of LQT needs further evaluation. A meta-analysis was conducted using systematic electronic searches of PubMed, Embase, and Cochrane Library. We assessed QTc reduction and cardiac events after Mexiletine treatment. Inclusion criteria: any study with no language restriction that diagnoses any type of LQTS, uses mexiletine treatment, and provides QTc comparison before and after treatment. Animal studies were excluded. The NIH Study Quality Assessment Tools and Newcastle-Ottawa Scale were used to evaluate bias. Data were analyzed using Review Manager 5.4 and MedCalc software. Nine studies (n=281) were included. Mexiletine reduced QTc by -64ms (mean difference [MD], -64.22; 95% confidence interval [CI] -76.13 to -52.30; p<.001; I^2 60%). Sensitivity and sub analyses showed consistent efficacy. In five studies (n=76), the number of patients with high-risk QTc (>500ms) significantly decreased (Risk Ratio [RR], 0.38; 95% CI 0.26-0.55; p<.001). Five studies (n=141) showed a significant reduction in cardiac events (RR, 0.25; 95% CI 0.14-0.44; p<.001). Two studies reported gastrointestinal (GI) problems and vertigo as side effects of mexiletine treatment. Mexiletine significantly reduces QTc and cardiac events in LQT2, LQT3, and aLQT patients. Mexiletine also significantly reduces the number of Long QT patients with high-risk QTc.

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Introduction

QT prolongation on an ECG can induce cardiac events and fatal arrhythmias. The causes of Long QT Syndrome (LQTS) can be divided into congenital and acquired.[1] The congenital LQTS is a result of pathogenic variants in the genes encoding ion channels, which cause delayed inactivation or loss of channel function. Acquired LQTS (aLQT) can be caused by acquired mechanisms such as electrolyte imbalance, drugs, or secondary to other medical conditions.[2] The prevalence of congenital LQTS is estimated to be approximately 1 in 2,500 to 1 in 10,000 individuals and has a high mortality rate without proper treatment, up to 21% within 1 year from the first syncope episode, and can be reduced to approximately 1% during 15 years of follow-up with treatment.[1,3] Six genes (KCNQ1, CALM1, CALM2, CALM3, KCNH2, and SCN5A) are already known as definitive genes for typical LQTS, while one gene (TRDN) has been found to have strong evidence for causality in LQTS. Additionally, nine genes (CACNA1C, KCNJ2, CAV3, ANK2, SCN4B, SNTA1, KCNE2, AKAP9, KCNJ5) are classified as having limited or disputed evidence as causative of LQTS.[4] KCNE1 was classified as having only limited evidence, and KCNE2 as having disputed evidence for causality in LQTS; both genes were classified as having strong evidence for specific risk alleles in predisposing to aLQTS.[5]

Lifestyle changes, beta-blocker, left cardiac sympathetic denervation (LCSD), and ICD implantation are the mainstay treatments for LQTS.[6] Gene-specific therapy is highly important in LQTS treatment since beta-blockers are not equally effective in all types of LQT (LQT3>LQT2>LQT1).[3] Mexiletine, a class Ib sodium channel blocker, has been utilized to a limited extent in LQTS patients, especially in LQT3.[6-7] Mexiletine use in other types of LQT remains a question as newer studies continue to be conducted.[8-10] To further evaluate the effect of mexiletine in other types of LQT, we performed a meta-analysis of currently available journal/literature.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to ensure the reporting quality. A systematic electronic search of PubMed, Embase, and Cochrane Library was conducted from database inception to February 8, 2025, without any language restrictions. The keywords used in the literature search were mexiletine, long QT syndrome, LQTS, acquired long QT, and acquired QT. The search strings used were (Mexiletine) AND (Long QT Syndrome OR Long QT OR LQTS OR acquired long QT OR acquired QT prolongation).

Inclusion Criteria and Exclusion Criteria

The inclusion criteria were as follows: any study with no language restriction that (1) diagnoses LQTS based on guidelines, with any type of LQT; (2) uses mexiletine treatment, which can be administered via the oral or IV route, given as chronic or acute treatment, and used as either an add-on or sole treatment; and (3) compares QTc before and after treatment. The exclusion criterion was whether the study was performed in a human or animal heart model.

Data Extraction and Quality Assessment

The authors (DIR and MIQ) independently screened the title and abstract to remove duplicates and then continued to review the full text to confirm and select the studies based on predefined inclusion and exclusion criteria. If there is a disagreement between authors, a third opinion from another author (CJC) will be considered. A predefined standard data extraction form was used to collect information, including author name, year, study design, population, LQT type, sex, age, mexiletine dose, route of administration, treatment combination, QTc before and after treatment, and cardiac events, which were performed by one author (DIR) and verified by another author (CJC). The study quality was assessed using the National Institutes of Health Study Quality Assessment Tool and Newcastle-Ottawa Scale (NOS).

Statistical Analysis

All data analyses were performed using Review Manager 5.4 and MedCalc software. Statistical significance was set at a p-value <0.05 was considered significant. Heterogeneity was considered using I^2 values of approximately 5% – 50% (mild), 50%–75% (moderate), and >75% (severe). If heterogeneity was moderate or severe, a random-effects model was selected, followed by a sub-analysis and sensitivity analysis. The primary outcomes of this study were QTc (mean ± SD) and cardiac events (RR) after mexiletine treatment. If the summary statistics were shown as median and interquartile range (IQR), the values of mean ± SD were estimated following the Cochrane guidelines. Studies with missing data necessary for other analyses were excluded. A sub-analysis was also performed for each LQT type. This study is shown as a forest plot.

Results

Study Characteristics

The study selection process is shown in the PRISMA flow diagram (Figure 1). Of the 358 identified studies, 29 duplicates were excluded. A total of 329 articles underwent title and abstract screening by two independent authors, and 9 studies were selected based on predefined inclusion and exclusion criteria and were included in the meta-analysis. Studies included were three focused on LQT3[11-13], one focused on LQT2[10], one focused on acquired LQT[9], and four evaluated more than one type of LQT[14-17], including one LQT2 study that involved two patients with multiple types of LQTS-associated variants (one patient with a variant in KCNQ1-mediated LQT1 and one patient with a variant in SCN5A-mediated LQT3).[14] The total population of this study was 281 patients. The population characteristics of the included studies are presented in Table 1.

Reduction of QTc and Cardiac Events

From 9 studies (n = 281), we evaluated the effect of mexiletine in reducing QTc and the number of cardiac events.[9-17] Mexiletine significantly reduced QTc by approximately -64ms (mean difference [MD], -64.22; 95% confidence interval [CI] -76.13 to -52.30; $p<0.001$; I^2 60%) (Figure 2A). After conducting a sensitivity analysis by removing one outlier study[17], the pooled mean difference for the QTc interval reduction with mexiletine treatment remained significant (MD, -67.66; 95% CI -75.93 to -59.40; $p<0.001$; I^2 0%). Some studies did not provide all the necessary data; therefore, we only included studies that contained the required information for other analyses to prevent potential bias. Mexiletine responders were defined as those with a QTc reduction ≥ 40 ms.[10,14] In five studies[9-10,12,14-15] (n = 140), the prevalence of QT reduction ≥40 ms was 74% (proportion 0.74; CI 0.55-0.90) (Figure 2B). The high-risk QTc was defined as QTc >500 ms.[12,14,17] From 5 studies[9,11-12,14-15] (n = 76), 56 (73%) patients had QTc >500 ms. After mexiletine treatment, the number of

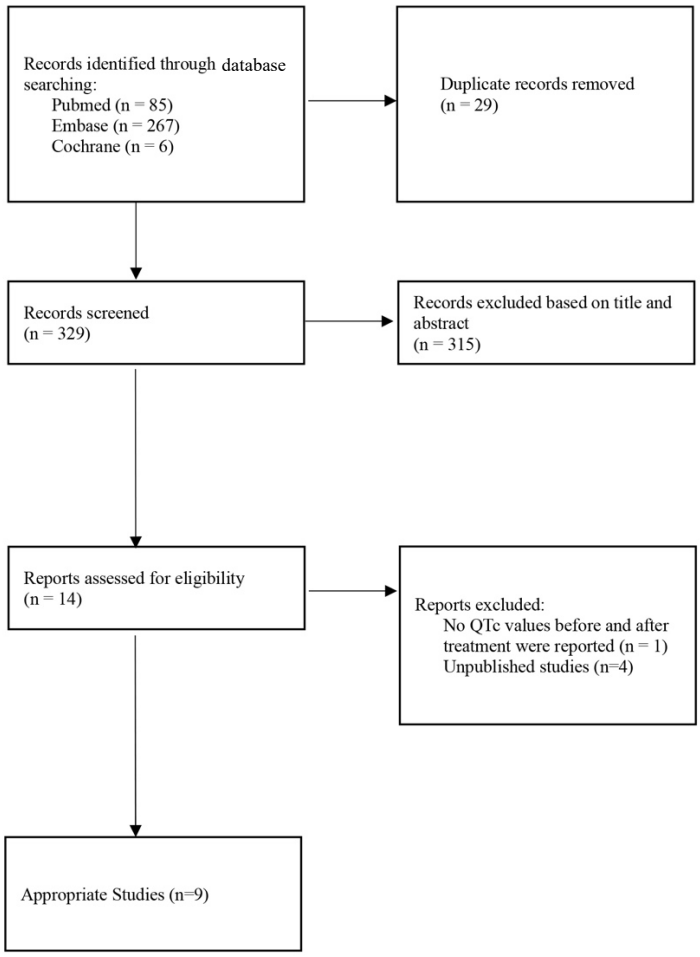


Figure 1. Flow diagram of literature searching.

Long QT patients with high-risk QTc significantly decreased to 21 (28%) patients (Risk Ratio [RR], 0.38; 95% CI 0.26-0.55; p<0.001) (Figure 2C).

Of the five studies[9-12,14] (n = 141) that included cardiac event reports, 48 (34%) patients had cardiac events before mexiletine treatment. The number of events was significantly reduced to 11 (7%) patients after mexiletine treatment (RR, 0.25; 95% CI 0.14-0.44; p<0.001) (Figure 2C).

Two studies reported side effects of mexiletine treatment.[10,14] One study[14] reported that 4 patients (33.3%) experienced gastrointestinal discomfort. Another study[10] reported 7 patients (22%) on the oral drug test had minor symptoms such as heartburn, nausea, vertigo, and epigastric pain, while 8 patients (9%) on chronic treatment experienced heartburn or nausea (In 4 cases, symptoms resolved simply by taking the treatment after meals and in the evening; in 4 other cases, therapy was suspended).

Table 1. Study characteristic and quality analysis.

Author, year of study	Study Design	Population Size	LQT subtype	Male/ female	Age (years)	Mexiletine Dosage and Route	Other treatment	Follow-up	Study Quality (NIH Quality assessment tools/NOS)
Bos J.M., et al (2019)[14]	Retrospective cohort study	12	LQT2; LQT 1 and 2; LQT 2 and 3	7/5	37.17 ± 25.5	4 to 6 mg/kg per dose/8 hours, oral	Beta-blocker 100%; LCSD 33%; ICD 8%	1.3 ± 0.9 years	Good/Good
Mazzanti A, et al (2016)[11]	Retrospective cohort study	34	LQT3	19/15	24.67 ± 27.86	average daily dose of 8 ± 0.5 mg/kg, oral	Beta-blocker 62%	59 months	Good/Good
Funasako M, et al (2016)[15]	**Prospective interventional cohort study**	31	LQT1; LQT2; LQT3	12/19	29 ± 18	2mg/kg, IV	NA	5 minutes after infusion	Good/Good
Ruan, et al (2007)[12]	**Prospective interventional cohort study**	5	LQT3	N/A	9.15 ± 6.15	6-8mg/kg/day, oral	Beta-blocker 100%	4.6 years	Good/Good
Schwartz P.J., et al (1995)[16]	**Prospective interventional cohort study**	15	LQT2; LQT3	6/9	20 ± 12	10 patients acute oral mexiletine 6 to 8 mg/ kg; 3 patients chronic oral mexiletine 12-16mg/kg/day, 1 patient acute and chronic therapy	Beta-blocker 47%; LCSD 40%; Pacemaker 13%	3 hours	Good/Good
Marwan B, et al (2015)[9]	**Prospective interventional cohort study**	12	aLQT	4/8	68 ± 10.14	Mexiletine (150 to 450 mg/day, oral	All patients receive TdP conventional treatment	2 hours	Good/Good
Dusi V, et al (2024)[17]	**Prospective interventional cohort study**	63	LQT1; LQT2; LQT3	N/A	N/A	N/A	Beta-blocker 100%	N/A	Fair/Poor
Blaufox A.D, et al (2012)[13]	Retrospective cohort study	13	LQT3	N/A	7.6 ± 5.9	7 mg/kg/day	N/A	1.2 years	Fair/Good
Crotti L, et al (2024)[10]	Retrospective cohort study	96	LQT2	45/53	16 ± 14	Acute oral drug test: 6 to 8 mg/ Kg; chronic oral therapy 9 ± 4 mg/kg	Beta-blocker 98%; LCSD 31%; ICD 29%	54 months	Good/Good

The quality of the studies was evaluated using the NIH Study Quality Assessment Tools and Newcastle-Ottawa Scale.
ICD, implantable cardioverter-defibrillator; IV, intravenous; LCSD, Left Cardiac Sympathetic Denervation; N/A, Not Available; TdP, Torsade de Pointes.

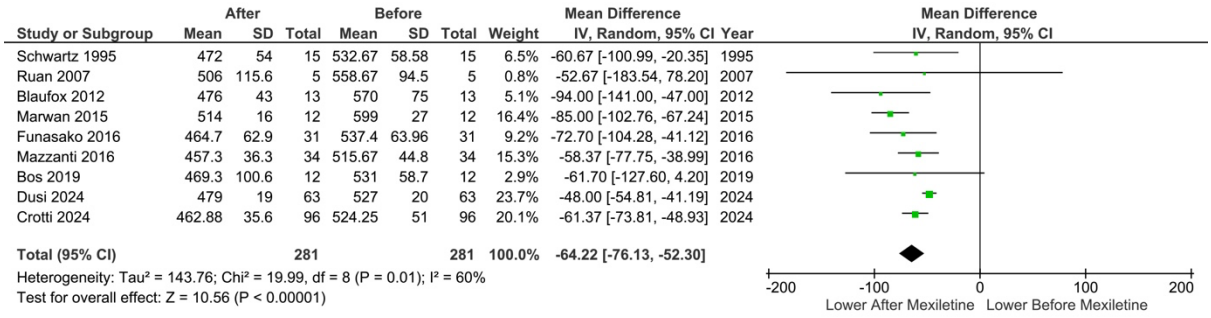
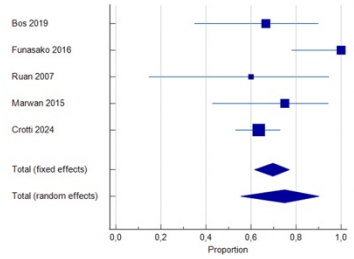


Figure 2A. MD with 95% CI of QTc reduction after mexiletine treatment.



Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Bos 2019	12	66,667	34,888 to 90,075	8,97	19,25
Funasako 2016	15	100,000	78,198 to 100,000	11,03	20,54
Ruan 2007	5	60,000	14,663 to 94,726	4,14	13,85
Marwan 2015	12	75,000	42,814 to 94,514	8,97	19,25
Crotti 2024	96	63,542	53,094 to 73,130	66,90	27,11
Total (fixed effects)	140	69,717	61,543 to 77,065	100,00	100,00
Total (random effects)	140	74,888	55,423 to 90,180	100,00	100,00

Figure 2B. Proportion of mexiletine responders with QTc reduction ≥40 ms.

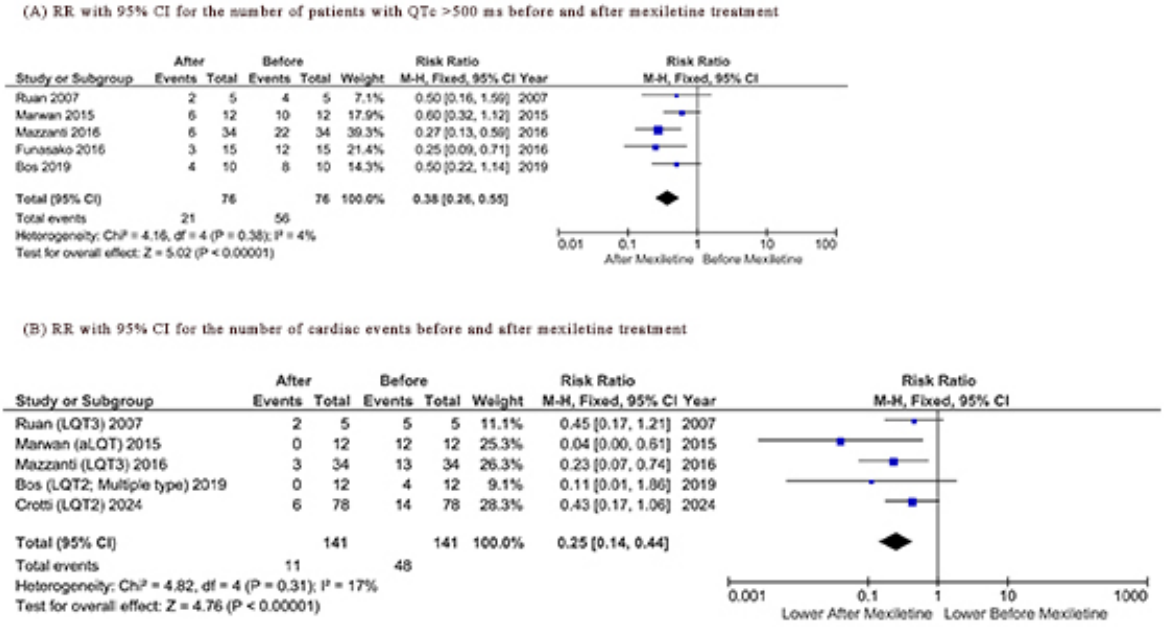


Figure 2C. (A) RR with 95% CI for the number of patients with QTc >500 ms before and after mexiletine treatment. (B) RR with 95% CI for the number of cardiac events before and after mexiletine treatment.

Effect on Different Subtypes of LQT

The heterogeneity in the main forest plot was moderate (60%), and a sub-analysis was needed to confirm the results for each subtype. There were 3 studies[10,14,16] that included the LQT2 population (n = 113). Mexiletine reduced QTc in the LQT2 population by approximately 60.2 ms (MD -60.22; 95% CI -72.05 to -48.38; p<0.001) (Figure 3). Five studies[11-13,15-16] included the LQT3 population (n = 75), with a QTc reduction of approximately 73 ms (MD, -72.64; 95% CI -87.31 − -57.98; p<0.001) after mexiletine treatment (Figure 3).

One study evaluated the aLQT, which was caused by stress-induced cardiomyopathy in 2 patients (16.7%), amiodarone in 5 patients (41.7%), levofloxacin in 2 patients (16.7%), dofetilide in 4

patients (33.3%), severe hypothyroidism in 1 patient (8.3%), and unidentified in 1 patient (8.3%).[9] Mexiletine reduced QTc in the aLQT population by approximately 85 ms (MD, -85.00; 95% CI -102.76 to -67.24; p<0.001).

There was no designated study focused only on the LQT1 population. Studies for rarer types of LQT were still limited to be included and evaluated in this meta-analysis.

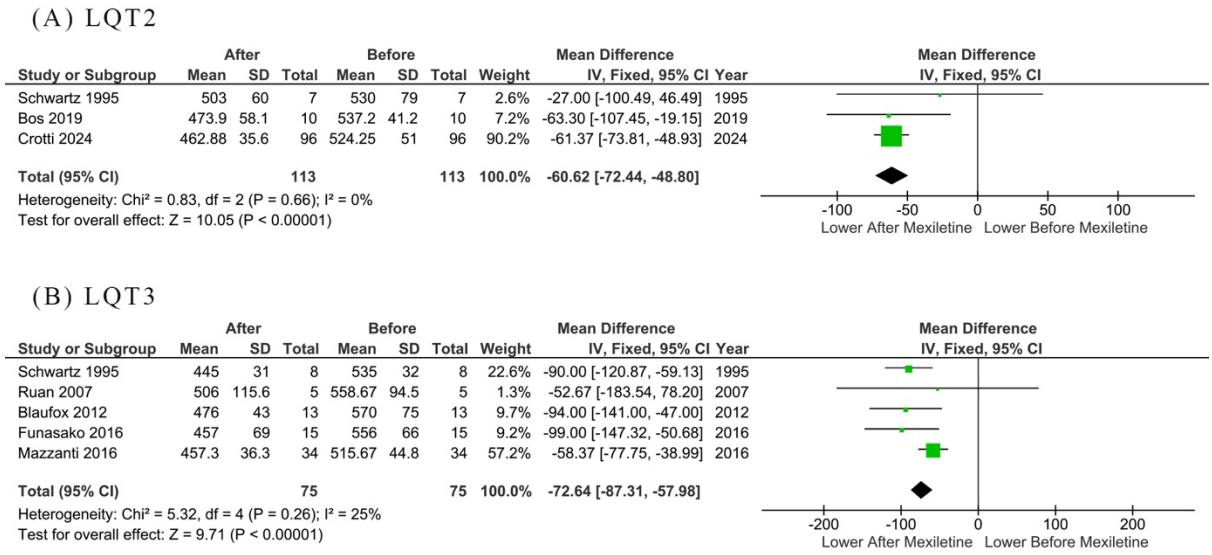


Figure 3. Forest Plot MD with 95% CI for each LQT type. (A) LQT2; (B) LQT3.

Discussion

The primary finding of this meta-analysis was that mexiletine significantly reduced QTc in LQT2, LQT3, and aLQT. Although the study showed moderate heterogeneity, the sub-analysis of each type of LQT indicated that mexiletine was able to reduce QTc significantly. The sensitivity analysis revealed that the removal of outliers reduced the heterogeneity from $I^2 = 60\%$ to $I^2 = 0\%$, indicating that these studies contributed substantially to the variability in the original analysis. These results confirm the robustness of our findings, supporting the efficacy of mexiletine in reducing QTc across LQT2, LQT3, and aLQT populations, with more consistent effects across studies. One study[17] was identified as an outlier and excluded from the final analysis due to concerns about the quality of the data, as the study did not provide adequate details. These limitations raise concerns about the reliability and accuracy of its findings.

Mexiletine works as a sodium channel blocker (Class Ib) that can reduce the prolonged sodium current (INa-L), as observed in LQT3 (a gain-of-function mutation in the SCN5A gene). The gating state of sodium channels may also be regulated by interactions among cardiac ion channels, which can be abnormal in conditions like LQT1 (Iks) and LQT2 (Ikr).[18-19] Mexiletine also reduces the action potential duration (APD) in cardiac myocytes by inhibiting the inward sodium current, which shortens the overall QTc and can benefit patients with LQT1, LQT2 and possibly other types of LQT.[19-20] The QTc reduction may occur due to the multi-hit model and the phenomenon of repolarization reserve, which suggests that repolarization is not regulated by only a single ion channel.[21-22] A similar result was shown in human-induced pluripotent stem cells from patients with LQT2, as well as in cardiomyocytes isolated from LQT2 rabbits (shortening the APD by 113 ms).[10] Mexiletine's efficacy was also demonstrated in patients with aLQT, which is primarily caused by the abnormality of potassium and sodium channels.[19,23-24] A study[24] reported on the efficacy of mexiletine in patients who were administered dofetilide. These results are similar to our meta-analysis (which also included a broader range of etiologies). One of the studies included in this meta-analysis reduced the risk of bias in aLQT management by administering mexiletine only after conventional treatments—especially the removal of the cause—were deemed ineffective, as evidenced by refractory torsade de pointes (TdP). The gene mutation is also suspected to be a risk factor in aLQT patients but has only been reported in a minority of cases.[5,25] The time-to-onset of aLQT may vary among drugs, which can affect the

timing of treatment withdrawal, making it difficult to prevent TdP and increasing the reliance on curative treatment.[26]

Mexiletine caused only slight changes in hemodynamic variables without significantly affecting the left ventricular systolic or diastolic function, resulting in a low incidence of significant side effects. This makes mexiletine a safer option for bradycardia-induced QT interval prolongation, as beta-blockers can worsen the condition.[19,23] Compared to other Class Ib drugs, mexiletine is more effective in treating LQTS patients.[8] Two studies[10,14] from this meta-analysis reported gastrointestinal (GI) problems and vertigo as side effects of mexiletine treatment. While mexiletine is generally considered safe, some patients experienced symptoms that required therapy suspension, indicating that further research on its safety profile is still needed.[10]

In this meta-analysis, 56 (73%) patients had QTc >500 ms (including LQT2, LQT3 and aLQT), which can increase both short- and long-term mortality.[1,27] Achieving a reduction in QTc is important, but reducing it to below 500 ms is crucial. In this study, 23 patients (30%) achieved this reduction (RR 0.45). In this meta-analysis, mexiletine was found to reduce the number of cardiac events. Similar results have been reported in patients with PVC or even in patients with recurrent VT/VF, which are refractory to other types of antiarrhythmics.[23,28] Based on ESC guidelines, so far, mexiletine is currently indicated only for LQT3 patients (Class I, Level of Evidence C recommendation).[19,29] This meta-analysis provides evidence to support the use of mexiletine for LQT2 and aLQT, and it is hoped that it will inspire further research into its use for other types of LQTS.

Limitation

The limitations of this meta-analysis are as follows: (1) The limited population size and number of studies hindered more detailed analyses, such as evaluating the effectiveness of mexiletine therapy in less common LQTS subtypes or assessing potential confounding factors influencing its therapeutic efficacy; (2) Further research with standardized dosing, therapeutic combinations, and routes of administration is required to provide stronger evidence regarding the effectiveness and safety profile of mexiletine therapy.

Conclusion

This meta-analysis concluded that mexiletine significantly reduced QTc and cardiac events in patients with LQT2, LQT3, and aLQT. Mexiletine also significantly reduced the number of Long QT patients with high-risk QTc. These findings support the use of mexiletine for LQT2 and aLQT and encourage further research into other LQTS types.

List of Abbreviations

aLQT	Acquired Long QT Syndrome
APD	Action Potential Duration
CI	Confidence Interval
ESC	European Society of Cardiology
GI	Gastrointestinal
ICD	Implantable Cardioverter Defibrillator
INa-L	Late Sodium Current
IQR	Interquartile Range
IV	Intravenous
LCSD	Left Cardiac Sympathetic Denervation
LQT1	Long QT Syndrome Type 1
LQT2	Long QT Syndrome Type 2
LQT3	Long QT Syndrome Type 3
LQTS	Long QT Syndrome
MD	Mean Difference
NIH	National Institutes of Health
NOS	Newcastle-Ottawa Scale
ORCID	Open Researcher and Contributor ID
PRISMA	Preferred Reporting Items of Systematic Reviews and Meta-Analyses
QTc	Corrected QT Interval
RR	Risk Ratio
TdP	Torsade de Pointes

Ethical Clearance

No new human participants or subjects were involved in this study (this meta-analysis used previously published data).

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

DIR – Conceptualization, Methodology, Formal analysis, Data collection, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Literature search, Software, Visualization.

MIQ – Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.

CJC – Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.
CA – Formal analysis, Investigation, Writing - Review & Editing, Supervision
MP – Formal analysis, Investigation, Writing - Review & Editing, Supervision
HSP – Formal analysis, Investigation, Writing - Review & Editing, Supervision.
MRA – Methodology, Writing - Review & Editing, Supervision.

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None.

Conflict of Interest
The authors declare that they have no conflicts of interest.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.
The software/code used in this study is available from the corresponding author upon reasonable request.

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