Neurological Sciences (2024) 45:3989–4001
https://doi.org/10.1007/s10072-024-07412-z

ORIGINAL ARTICLE

Effectiveness and safety of mexiletine versus placebo in patients with myotonia: a systematic review and meta-analysis

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Received: 19 June 2023 / Accepted: 16 February 2024 / Published online: 26 February 2024

Abstract

Background The rare nature of dystrophic and non-dystrophic myotonia has limited the available evidence on the efficacy of mexiletine as a potential treatment. To address this gap, we conducted a systematic review and meta-analysis to evaluate the effectiveness and safety of mexiletine for both dystrophic and non-dystrophic myotonic patients.

Methods The search was conducted on various electronic databases up to March 2023, for randomized clinical trials (RCTs) comparing mexiletine versus placebo in myotonic patients. A risk of bias assessment was carried out, and relevant data was extracted manually into an online sheet. RevMan software (version 5.4) was employed for analysis.

Results A total of five studies, comprising 186 patients, were included in the meta-analysis. Our findings showed that mexiletine was significantly more effective than placebo in improving stiffness score (SMD = −1.19, 95% CI [−1.53, −0.85]), as well as in reducing hand grip myotonia (MD = −1.36 s, 95% CI [−1.83, −0.89]). Mexiletine also significantly improved SF-36 Physical and Mental Component Score in patients with non-dystrophic myotonia only. Regarding safety, mexiletine did not significantly alter ECG parameters but was associated with greater gastrointestinal symptoms (GIT) compared to placebo (RR 3.7, 95% CI [1.79, 7.64]). Other adverse events showed no significant differences.

Conclusion The results support that mexiletine is effective and safe in myotonic patients; however, it is associated with a higher risk of GIT symptoms. Due to the scarcity of published RCTs and the prevalence of GIT symptoms, we recommend further well-designed RCTs testing various drug combinations to reduce GIT symptoms.

Keywords Dystrophic myotonia · Mexiletine · Non-dystrophic myotonia · Stiffness

Introduction

Myotonia is a defined as delay in the relaxation of muscles after contraction. It represents a hallmark clinical finding in several muscular disorders, including dystrophic (DM) and non-dystrophic (NDM) myotonia. The severity of myotonia ranges from mild to severe, disrupting daily tasks and patients' quality of life.

Myotonic dystrophies are a group of inherited, multisystem diseases with essential features of myotonia, muscle

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weakness, and early onset cataracts. There are two primary forms of dystrophic myotonia distinguished by their clinical and molecular presentations; myotonic dystrophy type I (DM1), commonly referred to as Steinert disease, and myotonic dystrophy type II (DM2), also recognized as proximal myotonic myopathy (PROMM). Despite its rarity, DM is the most common form of muscular dystrophy. As stated in his book, Harper reviewed prevalence studies of DM in Europe and estimated its gene frequency to be 1 in 7400 [1]. Davies et al. found that the prevalence of DM1 in the Japanese population was 5.5 per 100,000 [2]; moreover, DM is rarer in Sub-Saharan Africa [3]. For DM2, there are no currently established prevalence estimates. DM2 is generally thought to be rarer than DM1, but large-scale population studies to confirm this have not been conducted.

Steinert originally described DM1, and in 1992, its gene defect was found to be caused by an expansion of a CTG repeat located within the 3′ untranslated region of the myotonic dystrophy protein kinase gene (DMPK) [4, 5] with moderate correlation between longer CTG repeat expansion with earlier age of onset and more severe disease [6]. DM1 is usually presented as an adult-onset multisystem degenerative disease. In addition, it may affect fetal development and postnatal growth. DM1 can be subdivided into four types: (I) Congenital dystrophic myotonia (CDM) which is an autosomal dominant with the mother usually has adult-onset DM1, even though her symptoms may be so mild that she did not know she had the disorder. CDM is usually presented prenatally by reduced fatal movement, polyhydramnios, and ultrasound findings of talipes equinovarus or borderline ventriculomegaly. It also may be presented at birth with neonatal hypotonia and feeding or respiratory difficulty [7]. (II) Childhood DM occurs with an onset of 1 year to 10 years, which is usually presented mainly by cognitive and behavioral features and is not accompanied by muscular disease [8]. (III) Classic DM1: most patients develop symptoms in the 3rd or 4th decade of life, and its cardinal feature is myotonia, which involves specific muscle groups of the forearm, hand, tongue, and jaw. (IV) Mild DM1 caused by small CTG expansion and usually associated with mild myotonia, weakness, and early onset of cataract ($^{>}$ 40y).

After discovering of the DM1 gene defect, subsequent clinical studies—involving hundreds of patients exhibiting DM-like characteristics but with a pattern of proximal muscle involvement rather than distal and lacking the DM1 gene defect—introduced a new diagnostic label: DM type 2. Further studies identified that DM type 2 results from an unstable tetra nucleotide CCTG repeat expansion in intron 1 of the nucleic acid-binding protein (CNBP) gene (previously known as zinc finger 9 gene (ZNF9)) [9, 10]. The clinical picture of DM2 ranges from early adult-onset severe forms to very late-onset mild forms that are difficult to differentiate from normal aging with no evidence of congenital or childhood form [11]. DM2 has variable manifestations such as early onset cataract, various grip myotonia, thigh muscle stiffness, muscle pain—usually described as an exercise related pain compared to other chronic muscle disorders—and weakness [12, 13].

Non-dystrophic myotonias (NDM) are skeletal muscle ion channel disorders distinguished from DM by the absence of progressive weakness and eventual wasting of the muscle tissue in addition to the absence of systemic features. Recent data from electrophysiological and molecular biological studies led to a new classification of these disorders. Now, they are classified as chloride (Cl) or sodium (Na) channel diseases. The Cl channel disorders include autosomal-recessive myotonia Congenita (MC) (also called Becker's disease) and autosomal-dominant MC (also called Thomsen's disease). Na channel disorders are all autosomal-dominantly inherited diseases, and they comprise paramyotonia congenita (PC) and sodium-channel myotonia (SCM) [14].

Mexiletine is mainly used in treating atrial and ventricular arrhythmias as it is a class 1B antiarrhythmic drug. Due to mexiletine's high affinity to muscle sodium channels, its main mechanism of action is the blockade of fast sodium channels. Therefore, mexiletine is used to improve myotonia by promoting rapid deactivation of sodium channels, leading to sodium channel blockade. It may also produce an open channel block of late-opening channels at lower serum concentrations than those required to block closed and inactivated channels [15]. Additionally, mexiletine reduces the phase 0 maximal upstroke velocity of the action potential; thus, it increases the ratio of effective refractory period to action potential duration; but has a small impact on conduction. Although mexiletine does not affect skeletal muscle chloride channels, its beneficial effects in patients with myotonic chloride channel disorders, such as DM1 and MC, may be attributed to normal sodium channel blockade, which reduces motor unit repetitive firing [16].

As myotonic disorders are a rare, it is difficult to conduct large-sample trials to test the effectiveness, and safety of mexiletine. To evaluate the efficacy and safety of mexiletine, we conducted a meta-analysis of randomized controlled trials using mexiletine as an intervention compared to placebo in different types of myotonia patients.

Methods

We followed the PRISMA statement guidelines during the preparation of this systematic review and meta-analysis. We performed all steps in strict accordance with the Cochrane Handbook for Systematic Reviews of Intervention [17]. The protocol was registered on PROSPERO (CRD42023405146).

Search strategy and data sources

In this systematic review and meta-analysis, we searched the literature for relevant articles published until March 2023 in five electronic databases (PubMed, Cochrane, EBSCO, Web of Science, and Scopus) using relevant keywords; Our search strategy was ((Mexiletine OR (Oral lidocaine analog) OR (Class IB Sodium channel blocker) OR (N-hydroxymexiletine glucuronide)) AND (Myotonia OR (Myotonia dystrophica)). To avoid omitting relevant trials, we did not restrict the publication date during search, searched conference abstracts and references of included studies, and searched the literature again before writing the manuscript for any updated studies to avoid missing any articles. Our search considered research articles published in the English language only.

Inclusion and exclusion criteria

Inclusion criteria

Studies meeting the following criteria were included in our review:

(1) Randomized controlled trials (RCTs) comparing mexiletine with placebo to treat genetically or clinically diagnosed DM1 or NDM patients aged 16 years or older without comorbidities. (2) Studies published in English reported at least one of the primary outcomes: the stiffness score and hand grip myotonia, s, 90–5% with results about adverse events.

Exclusion criteria

Trials were excluded for the following reasons (1) study designs other than RCTs, (2) conference abstracts, (3) in vitro or animal studies, (4) trials used drugs other than mexiletine, additional drugs, other comparators instead of placebo or performed on healthy controls, (5) trials that did not conduct tests to evaluate the efficacy of mexiletine, and (6) reports that were duplicate publications or not published in English.

Study selection and data extraction

Selection process

After retrieving citations from electronic databases, we removed duplicates manually. Then the retrieved studies were screened in two steps; the first step was to screen titles and abstracts (using the Rayyan software [18]) of all included references independently by two authors at least to assess their relevance to our meta-analysis. The next step was to screen the full text of articles for final eligibility to this meta-analysis. Any disagreement between the two reviewers was resolved by discussion. If no agreement was reached, the final decision was made by a third reviewer.

Data extraction

For each trial, detailed information was carefully extracted from all the eligible trials, including first author name, year of publication, sample size, basic characteristics, study population, study design, study duration, study location, registration number, risk of bias domains, and outcome measures (primary and secondary outcomes). This process was performed manually by two independent authors using an online data extraction form.

Assessed outcomes

The primary outcomes of this study were stiffness score and hand grip Myotonia, 90–5%. Secondary outcomes were (1) short form-36 physical component score (SF-36 PCS), (2) short form-36 mental component score (SF-36 MCS), and (3) ECG outcomes: PR interval (ms), QRS interval (ms), and QTc interval (ms). Assessed adverse effect outcomes focused on patients experiencing gastrointestinal symptoms, headache, tremors, and other serious adverse events.

Risk of bias assessment

A group of three authors each independently assessed the risk of bias of included trials according to Cochrane Risk of Bias 2 of interventional studies reported in the Cochrane Handbook of Interventions [19], which encompasses sequence generation (selection bias), allocation concealment, blinding of patients and personnel (performance bias), blinding of outcome assessors (detection bias), missing outcome data (attrition bias), selective reporting of outcomes (reporting bias) and other sources of bias if present. Each domain was rated as a high, low, or unclear risk. Disagreements were resolved with collegial discussion. We could not assess the publication bias using funnel-plot-based methods because they are inaccurate for fewer than 10 studies reporting the same outcome.

Statistical analysis

Meta-analysis was performed in the presence of at least two included studies with available data for assessed outcomes using (RevMan software version 5.4) [20]. Regarding primary outcomes, data were reported in mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI) due to different outcome reporting scales. For dichotomous outcome data, the frequency of events and total number of patients were pooled as risk ratio

(RR) with 95% CI. If outcomes were presented at different time points, the last time point was considered for analysis. If means and standard deviations were not provided, we calculated them from standard errors, 95%CI, or other statistical indices using RevMan calculator. We adopted a fixed effect model rather than a random effect model, yielding a more accurate estimate of the pooled effect unless potential heterogeneity is present. Heterogeneity was roughly recognized by visual inspection of the forest plot and assessed by the chi-square test with a probability value of $P \leq 0.1$ and an I^2 value > 50% as an indicator of heterogeneity between included studies. We performed sensitivity analysis in multiple scenarios excluding one study in each scenario for each outcome in the meta-analysis to check the stability of the results. To solve detected heterogeneity, subgroup analysis was performed according to the type of myotonia into two subgroups (NDM and DM1).

Results

Search results and study characteristics

The systematic literature search identified 227 potentially relevant studies from five electronic databases (PubMed, Cochrane, Web of Science, Ebsco, and Scopus). After the removal of duplicates, 177 records remained. Titles and abstract screening were conducted to these 177 records and yielded 26 RCTs which met eligibility criteria. The remaining 26 studies were examined by full-text assessment; 21 studies were excluded with reasons. Therefore, five studies were included for qualitative and quantitative synthesis (Vicart et al. [21], Statland et al. [22], Stunnenberg et al. [23], Heatwole et al. [24], Logigian et al. [25]). Regarding [25], 2 trials were conducted on 30 participants; trial A included 20 participants receiving 150 mg TID from June, 2000 until March, 2002 while trial B included 20 participants (10 of them are from trial A) receiving 200 mg TID from May, 2001 until March, 2003. The process of searching as well as the number of included and excluded studies are shown in Fig. 1.

All included RCTs compared mexiletine to placebo in myotonic patients and were published between 2010 and 2021. Three studies [21–23] were conducted on patients with NDM; the remaining 2 studies [24, 25] included patients with DM1. The overall population included 186 participants with clinically or genetically diagnosed myotonia ((72) DM1, (114) NDM). Experimental groups were treated with mexiletine 200 mg TID except (Heatwole et al., Logigian et al. trial A) used 150 mg of mexiletine. At the same time, the control population received a placebo. In Vicart et al. study, the initial dosage of mexiletine or placebo was 200 mg per day, with increments of 200 mg every 3 days until a maximum dose of 600 mg per day was reached within one week. If participants experienced intolerable side effects, the dosage would be lowered or stopped altogether. The baseline characteristics of the included studies are shown in (Table 1).

Risk of bias and quality assessment

All included studies were considered at low risk of bias for allocation, randomization process, selective reporting outcomes and blinding of patients, personnel, and outcome assessors except 2 studies. Stunnenberg et al. received some concerns of risk of bias due to unclear information about completing missing data. Regarding Statland et al. possible unintentional unblinding of participants was reported during the study. It was noticed due to the significant increase in IVR treatment effect for stiffness in period 2 compared to period 1. This possibility was supported by a survey conducted after each period asking participants to guess their interventional group during the preceding period. (Figs. 2, 3).

Primary outcomes

Stiffness score was assessed in three of included studies [21–23] using different scales; interactive voice response diary (IVR) in [22, 23] and visual analog scale (VAS) in [21]. Meta-analysis results revealed that mexiletine could significantly improve stiffness in patients with NDM compared to the control group (SMD = −1.19, 95% CI [−1.53 to −0.85], $P < 0.00001$); Pooled studies were homogenous ($P = 0.92$, $I^2 = 0\%$) (Fig. 4).

Studies [22–25] assessed the hand grip myotonia outcome recorded as the time interval between 90 and 5% of peak grip force as measured by a computerized myometry program, averaged over conducted trials. Statland et al. were excluded from the meta-analysis process of hand grip myotonia outcome because its results were reported as a geometric-like mean estimate using the log $(t + 0.1)$ "normalizing" transformation unlike the remaining studies which used arithmetic mean. We conducted a sensitivity analysis for hand grip myotonia outcome as the forest plots showed high heterogeneity ($P < 0.0001$, $I^2 = 88\%$) but when we removed Stunnenberg et al., the heterogeneity was resolved (I^2 decreased from 88 to 0%) with ($P = 0.68$) in the meta-analysis under the random effect model. The removal of Stunnenberg et al. was explained by the different sub type of disease (NDM) in this study, while the other 2 studies included patients with DM1. Sensitivity analysis proved that mexiletine showed a significant improvement in hand grip myotonia in patients with DM1 (MD = −1.36 s, 95% CI [−1.83 to −0.89], $P < 0.00001$); pooled studies were homogenous ($P = 0.68$, $I^2 = 0\%$) (Fig. 5). The results of the sensitivity analyses on hand

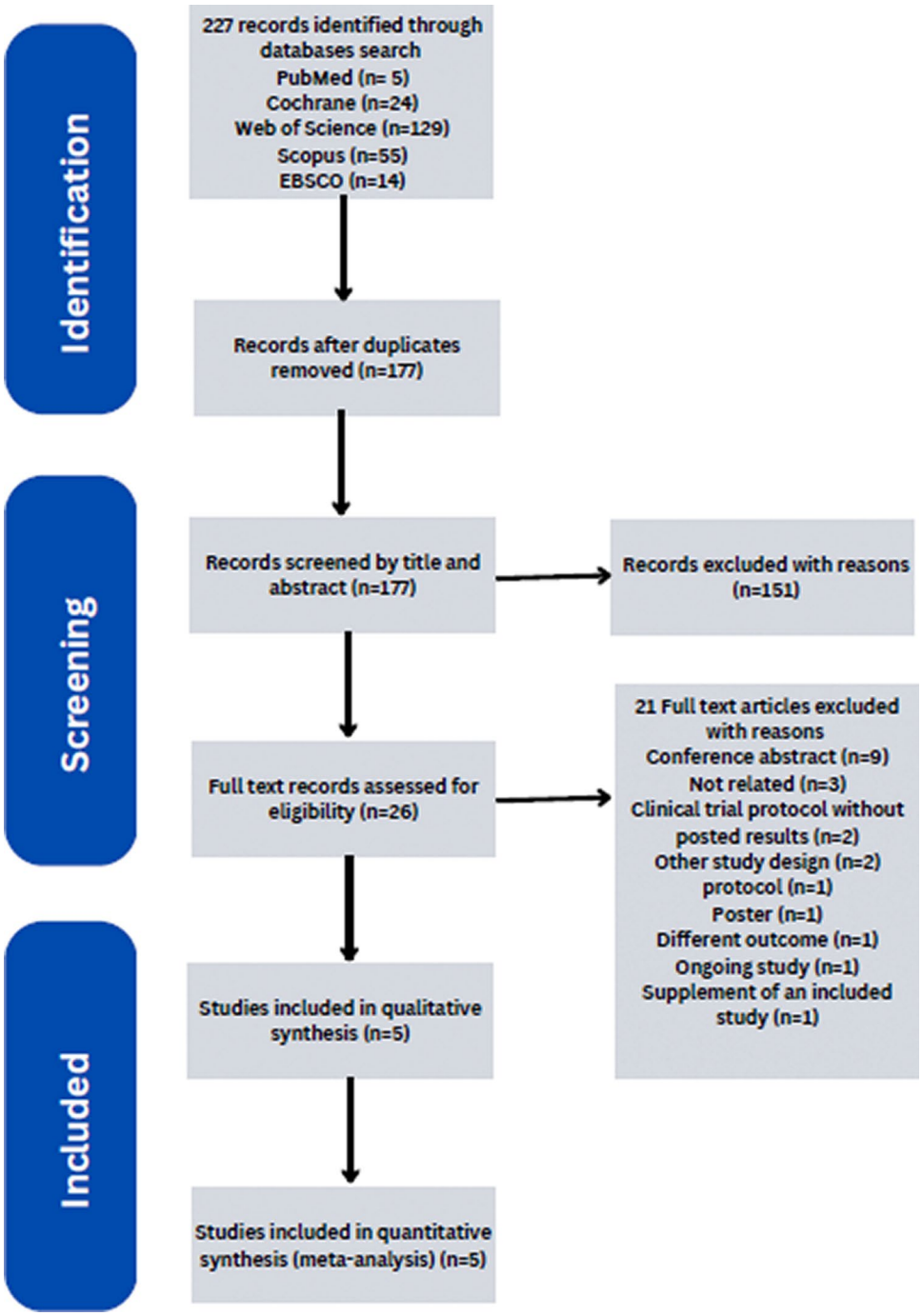

Fig. 1 PRISMA diagram of study selection process

grip myotonia, by excluding Stunnenberg et al., were consistent with the primary analysis; Both were statistically significant.

Secondary outcomes

ECG outcomes

The reason why ECG outcomes were reported in some of the included studies was attributed to the risk of developing some cardiac symptoms in DM patients. No significant differences were seen on ECG between the mexiletine and placebo groups in 2 of included studies [24, 25] in the atrioventricular conduction (PR) interval (MD = 1.12 ms, 95% CI [-3.65 to 5.89], $P = 0.65$), ventricular depolarization (QRS) interval (MD = 1.12 ms, 95% CI [-1.27 to 3.52], $P = 0.36$), and ventricular repolarization (QTc) interval (MD = 1.64 ms, 95% CI [-6.96 to 10.24], $P = 0.71$) (Fig. 6). The results of meta-analysis were homogenous and did not favor either of the two groups which indicates

Table 1 Study characteristics of included studies

Studies	Study years	Population	Treatment duration	Mexiletine treated	Placebo treated	Dose of mexiletine (mg)	Study location	Age mean (years)	Sex, female (%)	Outcome extracted	Adverse events extracted
Vicart et al	2021	-Male / Female -Age 18–65y -NDM(MC&PC)	P1: 18-22d P2: 18-22d WO: 4-8d	P1:13 P2: 12	P1: 12 P2: 12	200 TID	France	43.0	8(32)	-Stiffness score -(INQoL) Pain	GI symptoms
Statland et al	2008–2011	-Male/ Female -Age > 16y -NDM	P1: 4 w P2: 4 w WO: 1 w	P1: 29 P2: 29	P1: 30 P2: 25	200 TID	Multicentric study (USA, Canada, Italy, UK)	42.0	26 (44.1)	-Stiffness score -Hand grip myotonia -SF-36 PCS -SF-36 MCS	GI symptoms Headache tremors Insomnia Serious AE
Heatwole et al	2011–2017	-Age18–80y -Genetically confirmed DM1, iIGM > 1 s	6 m	21	21	150 TID	Rochester University, New York City (USA)	M: 42.1 P: 38.1	M:17 (81) P: 12 (57)	-Hand grip myotonia -SF-36 PCS -SF-36 MCS -(INQoL) overall -ECG outcomes	Headache Serious AE
Stunnenberg et al	2014–2016	-Adult patients with clinical phenotype and genetically confirmed NDM	Set1: 4w Set2: 4w WO: 1w	30#		200 TID	Netherlands	43.4	7(25.92)	-Stiffness score -Hand grip myotonia -SF-36 PCS -SF-36 MCS -(INQoL) overall	GI symptoms Headache tremors Insomnia Serious AE
Logigian et al.**	Trial A: 2000–2002 Trial B: 2001–2003	Male or female with myotonia dystrophy type 1, aged 18–80	P1: 7w P2: 7w WO: 4-8w	TA:11 TB: 10	TA: 9 TB: 10	TA: 150 TID TB: 200 TID	Rochester University, New York City (USA)	TA: 46.2 TB: 42.6	TA:7(35) TB:8(40)	-Hand grip myotonia -ECG outcomes	GI symptoms Headache Tremors

NDM, non-dystrophic myotonia; *DM1*, dystrophic myotonia type 1; *IGM*, isometric grip myotonia; *WO*, wash out period; *INQOL*, Individualized Neuromuscular Quality of Life

**Logigian et al. included 2 RCT with different doses (T1: 150 mg TID, T2: 200 mg TID) and 30 patients were enrolled in n the study (T1: 20 participants, T2: 20 participants); 10 participants were enrolled in both studies

#A series of aggregated, double-blind, randomized, placebo-controlled N-of-1-trials; 30 enrolled patients (19 CLCN1and 11 SCN4A genotype), 27 completed the study and 3 dropped out (1 because of a serious adverse events)

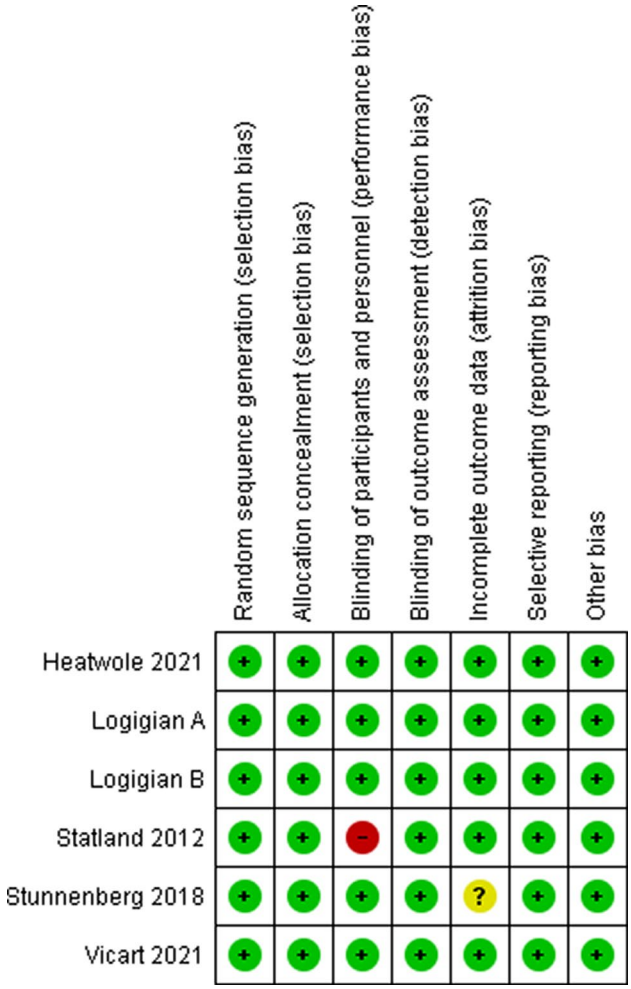

Fig. 2 Risk of bias summary for the included studies

that mexiletine does not cause significant changes on ECG in patients with DM1.

Short form-36 physical and mental component score

SF-36 PCS and SF-36 MCS outcomes were evaluated in only three of the included studies [22–24] using the Short-Form 36-Item Health Status Survey [26]. Due to marked heterogeneity for PCS ($P = 0.004$, $I^2 = 82\%$) and MCS ($P = 0.08$, $I^2 = 60\%$), subgroup analysis was performed for both outcomes according to the type of myotonia with random effect model and yielded 2 subgroups; The first group included NDM [22, 23] and the second one included DM1 [24]. Mexiletine significantly improved SF-36 PCS (MD = 6.83, 95% CI [4.29 to 9.37], $P < 0.00001$) and SF-36 MCS (MD = 5.19, 95% CI [2.88 to 7.49] $P < 0.00001$) in NDM patients (Figs. 7, 8).

Adverse events

In the five included studies, no significant differences in patients experiencing adverse events (AEs) were observed in different doses (150 mg or 200 mg TID) of mexiletine in comparison with placebo group. The results were calculated with the fixed effect model as no heterogeneity was detected among the studies. The frequent AEs were gastrointestinal symptoms, tremors, headaches, and other serious adverse events. The most common adverse events reported in the included RCTs were gastrointestinal symptoms. Incidence of gastrointestinal symptoms was higher among patients in the mexiletine groups than in the placebo groups (RR = 3.70, 95% CI [1.79 to 7.64], $P = 0.0004$); homogenous ($P = 0.12$, $I^2 = 45\%$) (Fig. 9). No significant difference was found between mexiletine and control groups regarding headache (RR = 1.12, 95% CI [0.54 to 2.33], $P = 0.76$); Pooled studies were homogenous ($P = 0.63$, $I^2 = 0\%$) (Fig. 10). Tremors were reported in only three of five included RCTs [22, 23, 25] and the overall risk ratio between the mexiletine and the placebo did not favor either of the two groups (RR = 4.44,

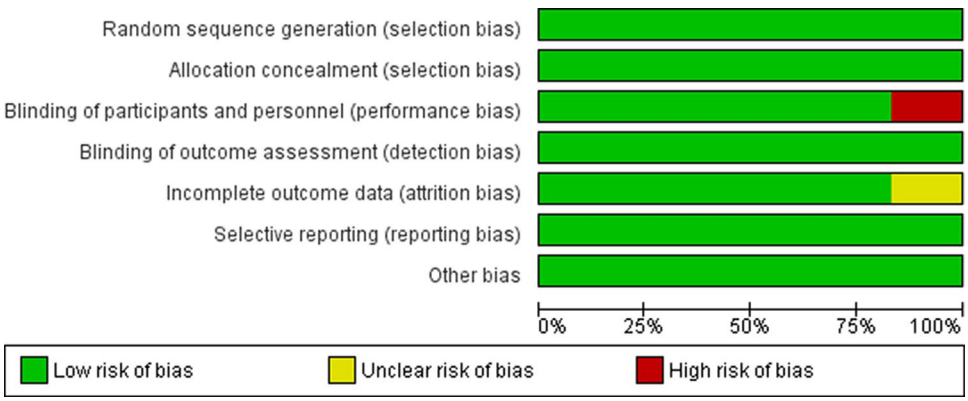

Fig. 3 Risk of bias graph for the included studies

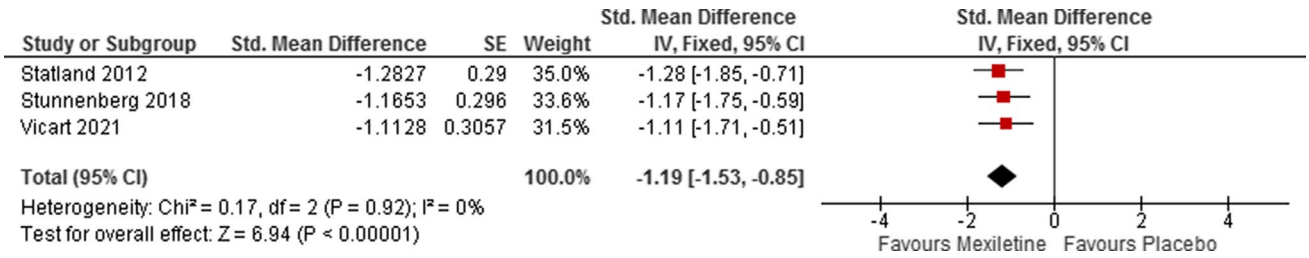

Fig. 4 Efficacy of mexiletine on stiffness score

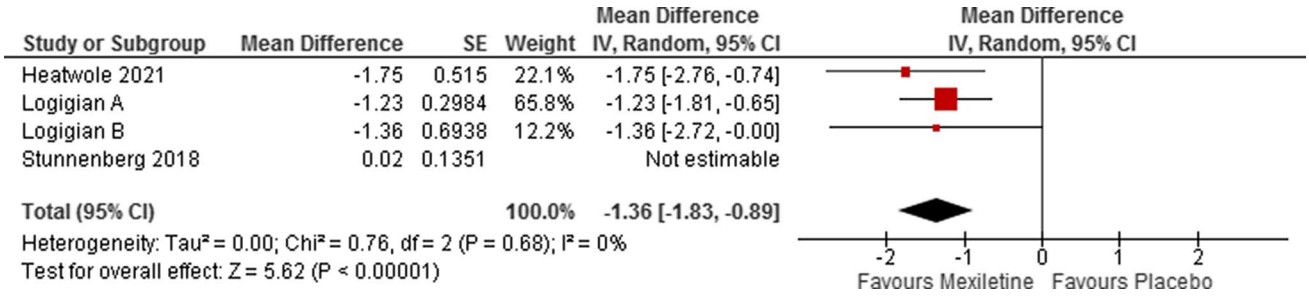

Fig. 5 Efficacy of mexiletine on handgrip myotonia (90–5%)

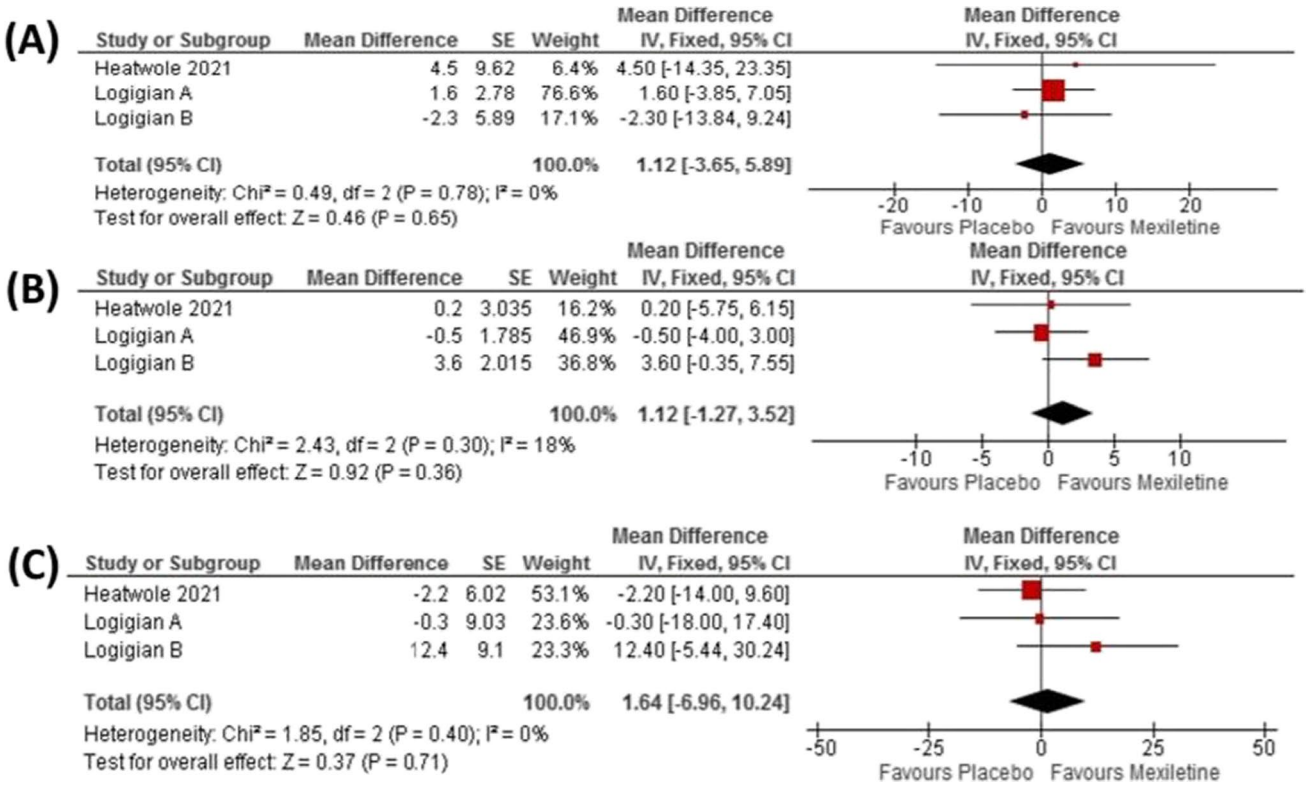

Fig. 6 shows the impact of mexiletine on ECG outcomes **A** PR interval, **B** QRS interval, and **C** Qtc interval.

95% CI [0.98 to 20.19], $P = 0.05$); homogenous ($P = 0.96$, $I^2 = 0\%$) (Fig. 11). Serious adverse events included (allergic skin reactions, strokes, or cervical fracture) and showed no statistically significant difference between the two groups (RR = 0.97, 95% CI [0.20 to 4.58], $P = 0.97$); studies were homogenous ($P = 0.67$, $I^2 = 0\%$) (Fig. 12).

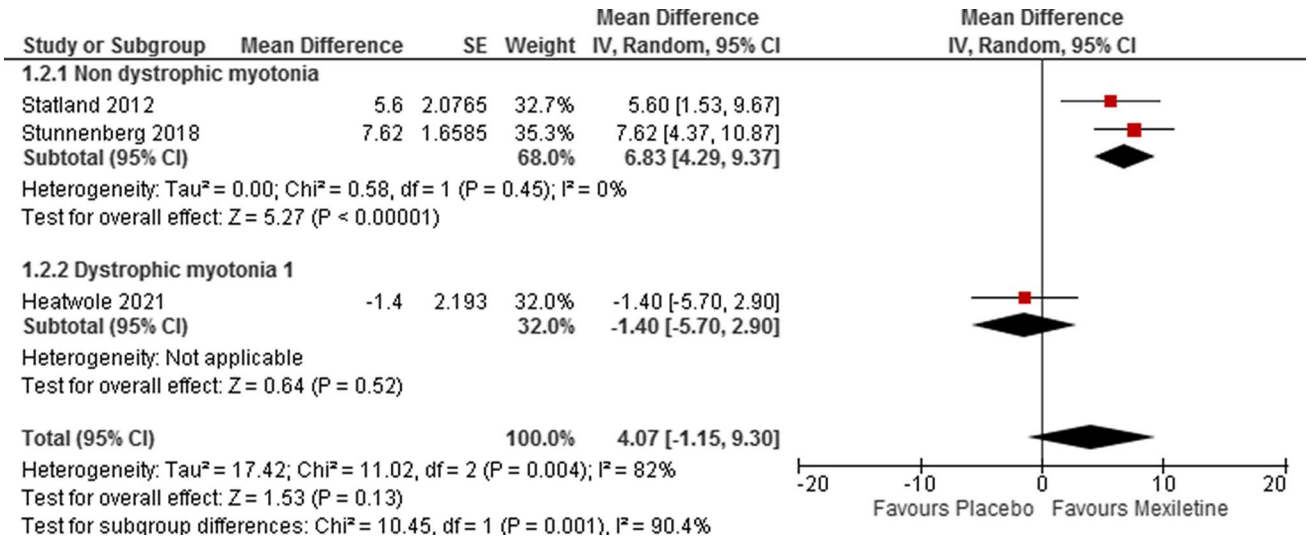

Fig. 7 Efficacy of mexiletine on SF-36 PCS

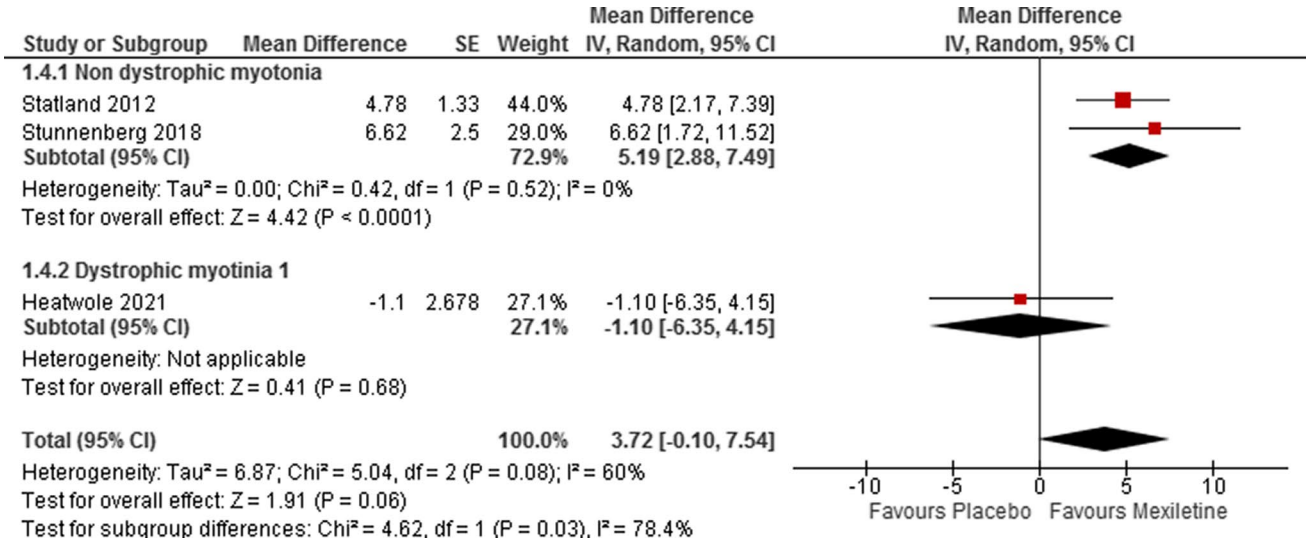

Fig. 8 Efficacy of mexiletine on SF-36 MCS

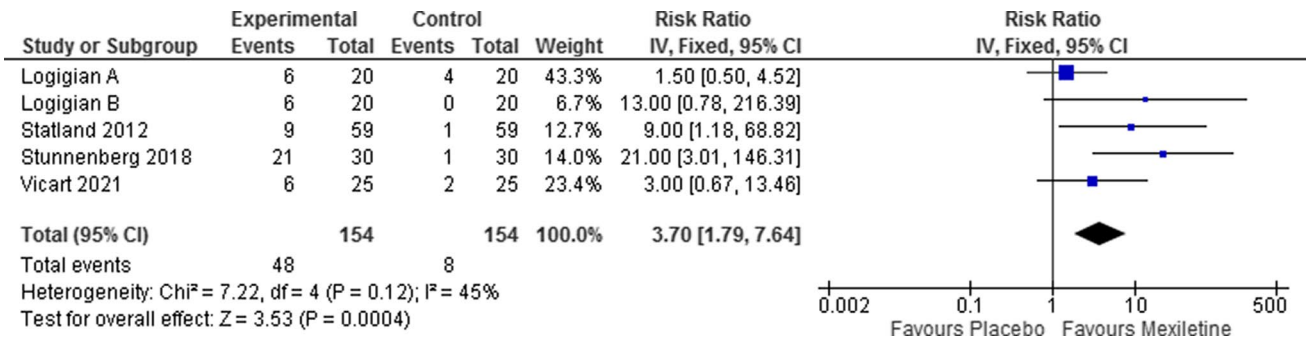

Fig. 9 Meta-analysis of GIT symptoms

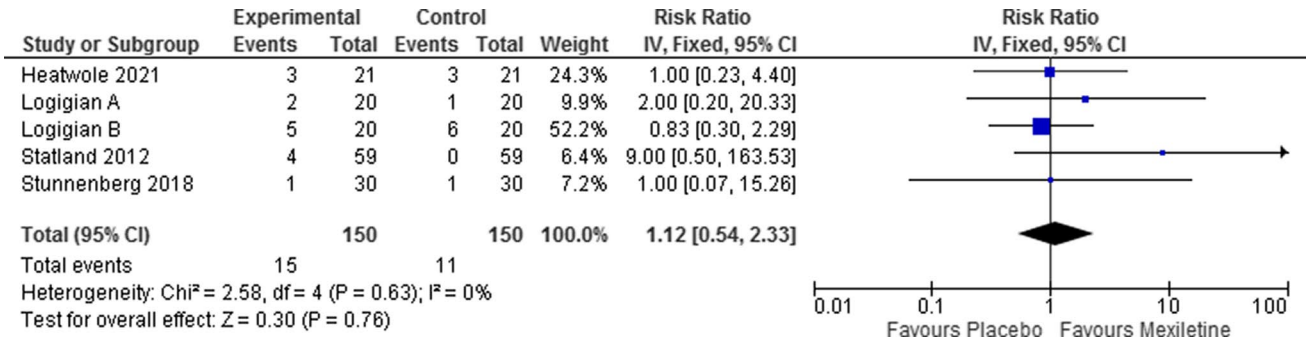

Fig. 10 Meta-analysis of headache

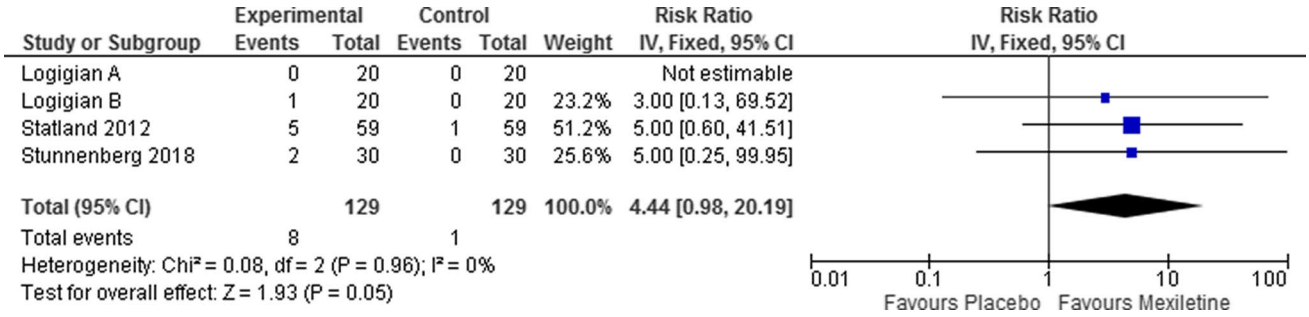

Fig. 11 Meta-analysis of tremors

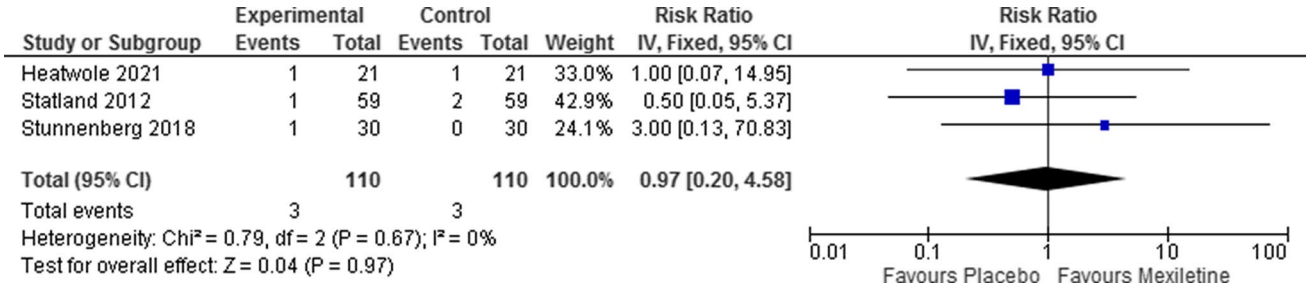

Fig. 12 Meta-analysis of serious adverse events

Discussion

In this systematic review and meta-analysis, we present all the currently reported knowledge on the efficacy and safety of mexiletine in patients with DM and NDM. Until 2009, there was a lack of randomized trials, and the existing studies were of poor methodological quality which did not provide adequate data leading to difficulty in performing a meta-analysis [27]. Simon D'Mello et al. [28] included 2 RCTs [22, 25] comparing Mexiletine against a placebo for review. The authors concluded that both studies were of good qualities (with some concerns about blinding in Statland et al.) but underpowered due to the small sample size. The recent systematic review [29], which addressed different skeletal muscle ion channelopathies, has included only 2 RCTs [22, 23] evaluating mexiletine and one evaluating lamotrigine in NDM patients [30]. It also concluded that there is still limited information about patients' response to the treatments. To the best of our knowledge, this study is the first systematic review and meta-analysis that investigated the effectiveness and safety of mexiletine for treatment of myotonic patients and there is not any related published meta-analysis. This gives this study a huge strength by adding this level of evidence on using mexiletine for different types of myotonia.

Myotonia is a rare clinical symptom presented in various genetic muscle channelopathy with a prevalence of 1 in 8000, 1 to 9 in 100,000, 0.2 to 7.4 in 100, and 1 in 250,000

for DM1, DM2, MC, and PC, respectively [31, 32]. Owing to this rarity, it was difficult to perform a large number of clinical trials on myotonia to get thorough evidence of any treatment intervention. Therefore, more research attention needs to be devoted to this field to evaluate the efficacy and safety of mexiletine for different clinical types of myotonia.

Other than mexiletine, several trials have evaluated alternative treatments indicating the potential efficacy of these drugs. The rationale behind using these drugs depends mainly on blocking Na channels, which reduces depolarization levels, leading to improvement of myotonia as in procainamide, disopyramide, phenytoin, quinine, tocainide, lamotrigine, and mexiletine. Others such as tricyclic antidepressants (clomipramine and imipramine) act by increasing the release of noradrenaline from sympathetic nerve fibers which stimulate B2 adrenergic receptors on skeletal muscle membrane leading to their inhibition [33, 34]. Taurine acts as a GABA receptor agonist, which enhances K and Cl membrane conductance reducing the hyper excitability of the muscles [35, 36]. Calcium channel blockers such as nifedipine block calcium channels in the skeletal muscle's surface membrane, decreasing intracellular calcium and preventing their contraction [37, 38]. The mechanism of all these drugs is just symptomatic that act as membrane-stabilizers.

Different active drugs were evaluated: quinine and procainamide in Leyburn et al. [39]; diazepam in Lewis et al. [40]; diphenylhydantoin and procainamide in Munsat et al. [41]; taurine in Durelli et al. [36]; mexiletine in Kratz et al. [42]; nifedipine in Grant et al. [43]; imipramine in Gascon et al. [33]; clomipramine in antonini et al. [44]; fenytoin, disopyramide, mexiletine, and tocainide in Kwiecinski et al. [45]. The comparator in these 9 RCTs was placebo, while Finlay et al. [46] evaluated procainamide against disopyramide. Unfortunately, those studies were of poor quality as they included a small number of participants (143 patients), which did not provide baseline characteristics of the individual participants or the two separated groups; five trials did not define explicit inclusion criteria and nine trials had no washout interval between the treatment periods. Other than RCTs, there were some studies that evaluated the efficacy of various drugs, as mentioned in Cochrane. Lamotrigine also showed potential efficacy and safety in improving myotonia in NDM patients as it is inexpensive and more available than mexiletine [30].

The meta-analysis results revealed that mexiletine is both effective and safe in myotonic patients compared to a placebo. The evaluation of efficacy comprises effects on stiffness score, hand grip myotonia, physical and mental component scores using the SF-36 health survey filled by participants. Mexiletine obviously reduced stiffness score in NDM. Despite myotonia being mild in patients with DM—it is not the main complaint of them—the effect of Mexiletine on stiffness in DM still needs to be evaluated.

Furthermore, mexiletine demonstrated a significant improvement in hand grip myotonia in patients with DM1. However, the effect of mexiletine on hand grip myotonia in non-dystrophic patients requires further investigation to obtain conclusive evidence. As in this review, the data from Statland et al. could not be included in the meta-analysis due to its representation by geometric mean. The only available data were from Stunnenberg et al., and the results were non-significant. This could be attributed to the different types of disease (DM1 and NDM) between the studies.

Mexiletine appears to improve the physical and mental components of SF-36 reported by non-dystrophic patients. On the other hand, the effect of mexiletine in dystrophic patients needs to be investigated in further studies because only one study evaluated it, and the results were insignificant.

Concerning safety evaluation, we focused on reporting ECG changes represented by QRS, QTc, and PR intervals since patients with DM1 are at risk of developing cardiac symptoms and at regular intervals to monitor for any cardiac side effects of mexiletine as it is used as anti-arrhythmic drug could have possible effects on cardiac conduction system. Clearly, results show no significant impact on ECG changes: QRS, QT, and PR intervals. As there is only one long period study [24], we call for more RCTs with long period of time to ensure the long-term cardiac effect in both DM and NDM patients. It is worth noting that there is one retrospective and one prospective studies confirmed no major ECG effects of mexiletine in NDM [47, 48].

Moreover, safety analysis shows no statistically significance regarding serious adverse events, headache, tremors. Despite its good safety profile, it showed a fourfold increase in GIT adverse events. The discontinuation rate due to side effects was not statistically significant and was roughly equal in both groups. Incorporating the safety data presented into mexiletine's product information is essential to inform patients and prescribers. Notably, the discontinuation rate due to side effects involved 7 out of the 186 patients across the five randomized controlled studies, representing less than 4%. Other reasons for discontinuation included non-compliance with follow-up; and lack of response to IVR calls. These factors were balanced between the two groups and explained by the intention to treat analysis.

The current study has some limitations. The number of available published RCTs was limited. This study could not be restricted to mexiletine-naïve patients due to rarity of the disease. Moreover, patients already treated with mexiletine showed hesitancy regarding stopping treatment for a long period. Some of the outcome measures showed heterogeneity, but this is explained by different types of myotonia among included studies. This heterogeneity was solved by subgroup and sensitivity analysis. Finally, there was one

ongoing study (NCT05017155) and three studies without results that could not be included.

We suggest conducting further well-designed controlled clinical trials comparing the effect of mexiletine against other drugs especially lamotrigine. Trials should be parallel ensuring adequate blinding by preventing guessing the treatment allocation. We also recommend for long period studies to determine mexiletine efficacy and safety on the long-term. Finally, it is recommended to use functional outcome measures such as stair test and chair test. To sum up, this systematic review and meta-analysis revealed that mexiletine is highly effective with a good safety profile at all evaluated doses for treating dystrophic and non-dystrophic myotonia.

Author contribution Research question was hypothesized by Elettreby. Literature search and validation of the question were done by all authors. Elettreby and Abo Elnaga were involved in planning and supervising the work. Alderbi and Fareed performed screening of studies and conflicts were resolved by Kamal and Sharkawy. Risk of bias assessment was done by Al Saied and Abo Elnaga. Elettreby, Abo Elnaga, and Alsaied performed data extraction from include studies and then revised by Kamal. Fareed and Alderbi designed the figures. Elettreby, Alsaied, Abo Elnaga, Kamal, and Sharkawy performed meta-analysis, while Alderbi and Fareed aided in interpreting the results. All authors discussed the results and worked on the manuscript.

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethical approval The manuscript does not contain clinical studies or patient data. This is a systematic review and meta-analysis for which no ethical approval or informed consents are required. All analyzed data were derived from existing peer-reviewed publications.

Conflict of interest The authors declare no competing interests.

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