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Drug treatment for myotonia (Review)

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[Intervention Review]

Drug treatment for myotonia

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ABSTRACT

Background

Abnormal delayed relaxation of skeletal muscles, known as myotonia, can cause disability in myotonic disorders. The main myotonic disorders are non-dystrophic myotonia and myotonic dystrophy. Non-dystrophic myotonia is a genetic muscle channelopathy predominantly causing myotonia. Myotonic dystrophic is a more systemic neuromuscular disorder causing myotonia as well as progressive myopathy and systemic manifestations, such as arrhythmias and cataracts. Myotonia manifests as stiffness, cramps, locking, pain, and fatigue, and can cause marked morbidity and disability. Sodium channel blockers, tricyclic antidepressive drugs, benzodiazepines, calcium antagonists, taurine, and prednisone may reduce myotonia. This is an update of a review first published in 2005 and updated in 2006.

Objectives

To review evidence from randomised controlled trials (RCTs) on the efficacy and tolerability of drug treatment in people with clinical myotonia due to myotonic disorders.

Search methods

We searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, and World Health Organization ICTRP on 29 March 2023. We handsearched the grey literature and contacted disease experts and antimyotonic drug manufacturers.

Selection criteria

We included RCTs involving participants with myotonia treated with any drug treatment versus no therapy, placebo, or any other active drug treatment. We included clinical trials where the reported primary outcome was a participant-reported measure of myotonia. We excluded non-RCTs and where myotonia may have been part of the condition (e.g. paramyotonia or Brody's disease). The primary myotonic conditions were myotonic dystrophy and non-dystrophic myotonia. Our primary outcome was participant-reported improvement in clinical myotonia. Our secondary outcomes were relaxation time, electromyographic relaxation time, adverse events, and quality of life.

Data collection and analysis

Review authors independently extracted the data onto standardised extraction forms. Three review authors independently assessed risk of bias and we collected adverse events data from the included trials. We assessed the certainty of the evidence using GRADE.

Main results

This review includes 17 double-blind or single-blind RCTs involving a total of 392 participants, 219 with myotonic dystrophy type 1 and 173 with non-dystrophic myotonia. Seven RCTs were newly identified and included in this update. Four of these RCTs investigated the effect of mexiletine or lamotrigine versus placebo in people with non-dystrophic myotonia. The remaining RCTs explored mexiletine in myotonic dystrophy.

Myotonic dystrophy

Mexiletine

No RCTs reported improvement in clinical myotonia according to validated scales. Mexiletine likely reduces hand grip relaxation time compared to placebo (mean difference (MD) 1.37 seconds better, 95% confidence interval (CI) 0.87 to 1.86; 2 RCTs, 56 participants; moderate-certainty evidence). Low-certainty evidence from four RCTs (91 participants) reported 55 adverse events with placebo and 84 adverse events with mexiletine. The most frequent adverse events with mexiletine were gastrointestinal symptoms, lethargy, and headache. There may be no difference in quality of life measures between mexiletine and placebo (36-item Short Form (SF-36) Physical Component Summary (PCS): MD −1.40, 95% CI −5.56 to 2.76; SF-36 Mental Component Summary (MCS): MD −1.10, 95% CI −6.17 to 3.97; 1 RCT, 38 participants; low-certainty evidence).

Non-dystrophic myotonia

Mexiletine

Mexiletine likely reduces myotonia compared to placebo using the Interactive Voice Response Diary Stiffness score (across both treatment periods: MD −3.12, 95% CI −3.75 to −2.49; 2 cross-over RCTs, 89 participants; moderate-certainty evidence). There is likely no effect on relaxation times with no differences in eye closure or clinical hand grip between mexiletine and placebo (2 RCTs, 89 participants; moderate-certainty evidence). Mexiletine likely improves quantitative hand grip (MD −0.11, 95% CI −0.18 to −0.04; 2 RCTs, 89 participants; moderate-certainty evidence). Mexiletine likely improves electromyographic-based outcomes, including degree of needle electromyographic myotonia detected (MD −0.67, 95% CI −0.23 to −1.11; 2 RCTs, 89 participants; moderate-certainty evidence). Low-certainty evidence from four RCTs (136 participants) reported 29 adverse events with placebo and 94 adverse events with mexiletine. The most frequent adverse events were gastrointestinal symptoms, lethargy, and headache. There may be improvement in quality of life with mexiletine compared to placebo (SF-36 PCS: MD 6.45, 95% CI 4.32 to 8.58; SF-36 MCS: MD 6.78, 95% CI 1.89 to 11.67, entire treatment period; 2 cross-over RCTs, 89 participants; low-certainty evidence).

Lamotrigine

No RCTs reported improvement in clinical myotonia according to validated scales. There may be improvement in relaxation time with lamotrigine treatment (hand grip: MD 2.80 (log) seconds better, 95% CI 2.09 to 3.51; eyelid closure: MD 2.30 (log) seconds better, 95% CI 1.79 to 2.81; 1 RCT, 22 participants; low-certainty evidence). Moderate-certainty evidence from one RCT (26 participants) reported 23 adverse events with placebo and 44 adverse events with lamotrigine. The most common adverse events with lamotrigine were headache, fatigue, and rash. Quality of life is likely to improve with lamotrigine compared to placebo (SF-36: MD 5.00 points better, 95% CI 3.12 to 6.88 points better; 1 RCT, 22 participants; moderate-certainty evidence).

Other medications

Other medications, including phenytoin, imipramine, procainamide, clomipramine, nifedipine, tocainide, diazepam, quinine, diphenylhydantoin, and taurine, were either ineffective or had uncertain evidence with small numbers. Trials were small, with the participant numbers ranging from nine to 59, with high risk of bias.

Authors' conclusions

More-recent trials are more robust, and well-conducted RCTs demonstrate moderate-certainty evidence for the efficacy of symptomatic treatments in non-dystrophic myotonias. Additionally, the data suggest that not all patients respond to therapy and research into aetiology and treatment options for non-responders is needed. Other agents that have not been tested in RCTs, such as acetazolamide, flecainide, ranolazine, and lacosamide, will need to be considered when planning future clinical trials. Moreover, the RCTs, in particular the small numbers of most trials, highlight the challenges in recruitment and design of robust trials in rare diseases, and research into trial design to improve recruitment in rare diseases will be important for future trials.

PLAIN LANGUAGE SUMMARY

What medicines are useful to treat myotonia (delayed muscle relaxation after contraction)?

Key messages

– Mexiletine appears to be safe and is likely an effective treatment for managing symptoms of myotonia (delayed muscle relaxation after a contraction) in people with non-dystrophic myotonia and it probably also slightly reduces myotonia in people with myotonic dystrophy.

– Lamotrigine may also reduce myotonia in non-dystrophic myotonia.

– More research and larger studies are needed to determine with certainty if lamotrigine is an effective treatment in both myotonic dystrophy and non-dystrophic myotonia.

What is myotonia?

Myotonia is delayed relaxation of muscles after they have contracted. It is a key symptom in a number of muscle diseases called myotonic disorders. These are genetic conditions that have a significant impact on quality of life and function, and include the conditions non-dystrophic myotonia (where there is no muscle wastage) and myotonic dystrophy (where there is muscle wastage).

Myotonia can affect skeletal muscles (muscles that are attached to bones by tendons and are responsible for movement; for example, hands, legs, and face) and is experienced as stiffness, cramps, locking, pain, and fatigue. There is currently no cure for myotonia but the symptoms can be treated with medicines called acetazolamide, phenytoin, mexiletine, lamotrigine, clomipramine, imipramine, and taurine (among others).

What did we want to find out?

This review looked at studies which tested the effectiveness of different medicines for treating myotonia.

What did we do?

We searched for well-designed studies that looked at treatments for myotonia. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 17 studies involving 392 people, of whom 219 had myotonic dystrophy type 1 and 173 had non-dystrophic myotonia. Seven studies were newly identified and included in this updated review, with 249 people (106 with myotonic dystrophy and 143 with non-dystrophic myotonia). Four of these studies looked exclusively at people with non-dystrophic myotonia and the effects of mexiletine or lamotrigine. Other studies explored mexiletine in people with myotonic dystrophy.

Based on these studies, mexiletine appears to be safe and is likely an effective treatment for the symptoms of myotonia in people with non-dystrophic myotonia. In myotonic dystrophy, mexiletine probably reduces myotonia slightly. Lamotrigine may reduce myotonia in people with non-dystrophic myotonia.

In general, both medicines were well tolerated. The most common unwanted effects of mexiletine were heartburn/reflux (a burning feeling in the chest that is caused by stomach acid coming up into your throat) and headache. The unwanted effects of lamotrigine included headache, skin rash and itching, and fatigue. These more-recent studies were better designed and conducted.

What are the limitations of the evidence?

Some of the included studies had sections that were not described well, and made the evidence less reliable. Studies of medicines other than mexiletine or lamotrigine were small or not well described. Our confidence in these medications was limited because the results varied widely between studies, and they involved only small numbers of people. Some studies did not clearly report how they were conducted and used methods that were likely to introduce errors in their results.

How up to date is this evidence?

The evidence is current up to March 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Mexiletine compared to placebo for myotonic dystrophy type 1

Mexiletine compared to placebo for myotonic dystrophy type 1

Patient or population: myotonic dystrophy type 1
Setting: medical centres within the USA and Poland
Intervention: mexiletine (150 mg or 200 mg 3 times daily)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mexiletine				
Improvement in participant-reported clinical myotonia according to validated scales Follow-up: NA	No validated outcome scales reported		—	0 (0 RCTs)	—	We are very uncertain about the effect as this outcome was not reported according to any validated scales. 1 study (42 participants) reported no beneficial effects of mexiletine 150 mg 3 times daily compared to placebo in hand/finger myotonia visual analogue scale score at 6 months, a scale which is not validated in this patient cohort.
Relaxation time (after maximal contraction of hand grip using a dynamometer, a computerised capture system that records the time taken in seconds to relax from 90% to 5% of maximal force determined using automated analysis software) Follow-up: 4 weeks to 6 months	Mean relaxation time ranged from 2.55 seconds to 4.1 seconds in the placebo groups	Mexiletine 150 mg 3 times daily **MD 1.37 seconds better** (1.86 seconds better to 0.87 seconds better)	—	56 (1 parallel RCT and 1 cross-over RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
	Mean relaxation time was 2.63 seconds in the placebo group	Mexiletine 200 mg 3 times daily **MD 1.36 seconds better** (0.63 seconds better to 2.09 seconds better)	—	18 (1 cross-over RCT)		
EMG relaxation time	No studies reported the outcome					

Follow-up: NA						
Occurrence of adverse events Follow-up: 4 weeks to 6 months	55 adverse events reported in placebo group	84 adverse events reported in mexiletine group	—	91[b] (1 RCT and 3 cross-over RCTs)	⊕⊕⊖⊖ **Low**[c,d]	The most frequent adverse events were gastrointestinal symptoms, lethargy, and headache. Rates of specific adverse events between mexiletine and placebo were similar.
Quality of life: SF-36 (0–100) Follow-up: 6 months	No differences between mexiletine 150 mg 3 times daily and placebo in terms of: • SF-36 PCS (MD −1.40, 95% CI −5.56 to 2.76) • SF-36 MCS (MD −1.10, 95% CI −6.17 to 3.97)		—	38 (1 RCT)	⊕⊕⊖⊖ **Low**[a,e]	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **EMG:** electromyographic; **MCS:** Mental Component Summary; **MD:** mean difference; **NA:** not applicable; **PCS:** Physical Component Summary; **RCT:** randomised controlled trial; **SF-36:** 36-item Short Form.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to potential risk of bias (high risk of selective reporting bias in Heatwole 2021).
[b]Overlap of 10 participants who participated in both Logigian 2010a and Logigian 2010b. Adverse events were not reported separately for 9 participants with myotonic dystrophy type 1 in Kwiecinski 1992 (also 21 participants with non-myotonic dystrophies).
[c]Downgraded one level due to risk of bias (high risk of detection and attrition bias in Kwiecinski 1992 and high risk of bias selective reporting in Heatwole 2021).
[d]Downgraded one level due to imprecision: number of events only reported, number of participants experiencing adverse events unclear due to how the results were reported and due to overlap of participants in the studies.
[e]Downgraded one level due to imprecision: wide confidence intervals.

Summary of findings 2. Mexiletine compared to placebo for non-dystropic myotonias

Mexiletine compared to placebo for non-dystropic myotonias

Patient or population: non-dystropic myotonias
Setting: outpatient clinics and medical centres within North America (USA and Canada) and Europe (England, France, Italy, Poland, Netherlands)
Intervention: mexiletine (150 mg or 200 mg 3 times daily)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mexiletine				
Improvement in participant-reported clinical myotonia according to validated scales: stiffness reported on Interactive Voice Response System (0–9) Follow-up: 38 days to 44 weeks	Stiffness was reduced in the mexiletine group compared to the placebo in: • the first treatment period: MD −1.68 (95% CI −2.66 to −0.70; 1 RCT, 59 participants) • the second treatment period: MD −3.67 (95% CI −4.65 to −2.69; 1 RCT, 59 participants) • across both treatment periods: MD −3.12 (95% CI −3.75 to −2.49; 1 RCT, 30 participants)		—	89 (2 cross-over RCTs)	⊕⊕⊕⊖ **Moderate**[a,b]	—
Relaxation time (seconds) Follow-up: 38 days to 44 weeks	There was no difference between mexiletine and placebo in: • eye closure: MD −1.04 (95% CI −2.76 to 0.69; 2 RCTs, 89 participants) • clinical hand grip: MD −0.62 (95% CI −1.37 to 0.14; 2 RCTs, 89 participants) There was improvement in the mexiletine group compared to the placebo group in quantitative hand grip (after maximal contraction of hand grip using a dynamometer, a computerised capture system records the time taken in seconds to relax from 90% to 5% of maximal force determined using automated analysis software): MD −0.11 (95% CI −0.18 to −0.04; 1 RCT, 59 participants)		—	89 (2 cross-over RCTs)	⊕⊕⊕⊖ **Moderate**[c]	—
EMG relaxation time: needle EMG Follow-up: 38 days to 44 weeks	Improvement in the mexiletine group compared to the placebo group in: • needle EMG ADM: MD −0.57 (95% CI −0.81 to −0.32; 1 RCT, 59 participants) • needle EMG TA: MD −0.46 (95% CI −0.68 to −0.25; 1 RCT, 59 participants) • myotonic discharges on needle EMG: MD −0.67 (95% CI −0.23 to −1.11; 1 RCT, 30 participants)		—	89 (2 cross-over RCTs)	⊕⊕⊕⊖ **Moderate**[d]	—
Occurrence of adverse events Follow-up: 38 days to 44 weeks	29 adverse events were reported in placebo group	94 adverse events were reported in mexiletine group	—	136[d] (4 cross-over RCTs)	⊕⊕⊖⊖ **Low**[e]	The most frequent were gastrointestinal adverse effects and headache

Quality of life **SF-36 (0–100)** Follow-up: 38 days to 44 weeks	There was an improvement in the mexiletine group compared to the placebo group in: • SF-36 PCS: MD 6.45 (95% CI 4.32 to 8.58; 2 RCTs, 89 participants) • SF-36 MCS: MD 10.40 (95% CI 0.80 to 20.00, second treatment period; 1 RCT, 59 participants) • SF-36 MCS: MD 6.78 (95% CI 1.89 to 11.67, entire treatment period; 1 RCT, 30 participants) There was no difference between the mexiletine and placebo groups in SF-36 MCS (MD −0.35 95% CI −5.75 to 5.05, first treatment period; 1 RCT, 59 participants)	—	89 (2 cross-over RCTs)	⊕⊕⊖⊖ **Low**[a,b,f]	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADM: abductor digiti minimi; **CI:** confidence interval; **EMG:** electromyographic; **MCS:** Mental Component Summary; **MD:** mean difference; **PCS:** Physical Component Summary; **RCT:** randomised controlled trial; **SF-36:** 36-item Short Form; **TA:** tibialis anterior.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Due to the differences in reporting of results (i.e. separately by treatment period or for both treatment periods combined), we have not pooled the results of the two trials in meta-analysis; results by treatment period and overall are presented separately.
[b]Downgraded one level for inconsistency: due to differences in the reporting of results because of evidence of carry-over, results of the two trials were presented separately.
[c]Downgraded one level due to inconsistency: substantial heterogeneity between trials in meta-analysis (I^2 = 68% and 80%).
[d]Downgraded one level due to applicability: needle EMG is a user-dependent measure of EMG relaxation time, which has not been clinically validated.
[e]Downgraded two levels due to serious imprecision: number of events only reported, number of participants experiencing adverse events unclear due to how the results were reported and events in the placebo group were less frequently reported.
[f]Downgraded one level due to imprecision: wide confidence intervals.

Summary of findings 3. Lamotrigine compared to placebo for non-dystropic myotonias

Lamotrigine compared to placebo for non-dystropic myotonias
Patient or population: non-dystropic myotonias **Setting:** neuromuscular centres in Copenhagen and Aarhus, Denmark **Intervention:** lamotrigine (300 mg daily) **Comparison:** placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with lamotrigine				
Improvement in participant-reported clinical myotonia according to validated scales Follow-up: NA	No results of lamotrigine compared to placebo were reported using validated scales		—	0 (0 RCTs)	—	We are very uncertain about the effect as comparative data were not reported using a validated scale. 1 cross-over RCT (26 participants) reported a decrease in MBS score following 1–3 weeks of lamotrigine treatment (results not reported for the placebo group).
Relaxation time (seconds, log transformed) Follow-up: 1–3 weeks	Not estimable (see comment)	Hand grip (time from the command 'open' to fully stretching of all 5 fingers) was **MD 2.80 (log) seconds better** (3.51 (log) seconds better to 2.09 (log) seconds better)	—	22 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[a,b]	The risk in the placebo groups was not estimable due to cross-over design of the study.
	Not estimable (see comment)	Eyelid closure (time from closure to fully open eyes) was **MD 2.30 (log) seconds better** (2.81 (log) seconds better to 1.79 (log) seconds better)				
EMG relaxation time Follow-up: NA	No studies reported the outcome					
Occurrence of adverse events Follow-up: 1–3 weeks	23 adverse events reported among 8 participants in placebo group	44 adverse events reported among 13 participants in lamotrigine group	—	26 (1 cross-over RCT)	⊕⊕⊕⊖ **Moderate**[a]	The most common adverse effects in lamotrigine group were headache, fatigue, and rash.
Quality of life: SF-36 (overall health status) (0–100)	Not estimable (see comment)	**MD 5.00 points better** (3.12 points better to 6.88 points better)	—	22 (1 cross-over RCT)	⊕⊕⊕⊖ **Moderate**[a]	The risk in the placebo groups was not estimable due to cross-over design of study.

Follow-up: 1–3 weeks				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **EMG:** electromyographic; **MBS:** Myotonia Behaviour Score; **MD:** mean difference; **RCT:** randomised controlled trial; **SF-36:** 36-item Short Form.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to imprecision: an initial sample size of 42 participants was calculated; however, after interim analysis with defined stopping criteria, the study was stopped at 26 participants. It is unclear whether the study was powered to detect differences based on the sample size recruited.
[b]Downgraded one level due to applicability: log transformed results only were available; magnitude of effect was difficult to interpret.

BACKGROUND

Clinical myotonia refers to delayed muscle relaxation after voluntary or evoked muscle contraction (Logigian 2005; Ptácek 1998). It is a cardinal feature of myotonic disorders including myotonic dystrophy and the non-dystrophic myotonias. Myotonia may be present in any skeletal muscle. Clinical examination reveals action myotonia and percussion myotonia, or both. Action myotonia and percussion myotonia are best tested in the hand muscles: following voluntary grip, the ability to relax the grip is delayed (action myotonia or grip myotonia); or mechanical stimulation, for example, a blow with the percussion hammer on the thenar muscles will also contract the muscle for a few seconds (percussion myotonia). Furthermore, an acute muscle contraction may give a transient decline in muscle force (transient paresis) (Drost 2001; Ricker 1978).

A number of conditions are associated with delayed relaxation of muscles in a way that resembles myotonia but without the characteristic electrophysiological features of true myotonia; they are termed 'pseudomyotonia' (Harper 2001). Because such pseudomyotonia may have a different physiological basis from true myotonia, we excluded these conditions from our review. They include Hoffman's disease (myotonia in hypothyroidism), Brody's disease (sarcoplasmic reticulum-Ca^{2+}ATPase deficiency), neuromyotonia, neuroleptic malignant syndromes, and tetanus. Schwartz-Jampel syndrome (chondrodystrophia myotonia) was also excluded because myotonic activity in this disease persists during general anaesthesia, which does not happen in true myotonia (Fowler 1974). True myotonia syndromes included in this review are discussed below.

Description of the condition

Myotonic dystrophy

Myotonic dystrophy type 1 is an autosomal-dominant disorder in which myotonia is accompanied by a characteristic pattern of muscle weakness and by the involvement of several organs (Cürschmann 1912; Harper 2004; Steinert 1910). This condition is caused by an expanded CTG (cytosine-thymine-guanine) trinucleotide repeat in the *DMPK* gene on chromosome 19q (Brook 1992; Harley 1992). The inheritance is characterised by anticipation, that is, earlier and more severe onset of the disease in successive generations (Howeler 1989). The prevalence of myotonic dystrophy type 1 varies from 2 per 100,000 to 12 per 100,000 (Emery 1991). Myotonic dystrophy type 2 differs from type 1 in its predominant proximal muscle weakness. Therefore, it was originally named proximal myotonic myopathy (Moxley 1996; Ricker 1999). Myotonic dystrophy type 2 is caused by an increased CCTG repeat in the *ZNF9* gene on chromosome 3. We have included people with clinical myotonia due to both types of myotonic dystrophy. Of note, myotonic dystrophy type 1 is a multisystemic condition classically causing cardiac conduction deficits, diabetes, and cataracts (Harper 2004; Turner 2010). However, more broad systems are involved with examples including cardiomyopathy, endocrine dysfunction, and cognitive dysfunction (Turner 2010).

Non-dystrophic myotonias

Clinically, non-dystrophic myotonias have myotonia with or without periodic paralysis (Rüdel 1994); however, fixed weakness occurs rarely. Onset of non-dystrophic myotonias is usually in the first or second decade of life. Myotonia is experienced as stiffness, cramps, pain, and locking (Vivekanandam 2020a). It can lead to falls, causes fatigue, and has a significant impact on education and employment.

Myotonia congenita

Myotonia congenita is caused by variants in the *CLCN1* gene coding for the skeletal muscle chlorine channel. It can be inherited in an autosomal-recessive manner (previously called Becker's disease) (Becker 1970; Becker 1977), or in an autosomal-dominant manner (previously called Thomsen's disease) (Thomsen 1876). People with autosomal-recessive myotonia congenita tend to have a more severe phenotype and may also experience transient weakness (Drost 2001; Ricker 1978). The disorders are caused by a mutation in the skeletal muscle chloride channel gene (*CLCN1*) on chromosome 7q (Fontaine 1997; George 1993; Koch 1992). The prevalence of myotonia congenita due to chloride channel variants varies in different studies between 2 per 100,000 and 7.3 per 100,000 (Baumann 1998; Becker 1977; Horga 2013; Rüdel 1994; Vivekanandam 2023).

Myotonia predominantly affects the legs, hands, and axial muscles but can affect any skeletal muscle. Myotonia is often triggered by initiation of movement, stress, or prolonged rest. Repeated contraction and relaxation may improve myotonia as well as muscle force, which is called the 'warm-up' phenomenon (Vivekanandam 2020b).

Paramyotonia congenita and sodium channel myotonia

Paramyotonia congenita and sodium channel myotonia are caused by a mutation in the muscle sodium channel gene (*SCN4A*) on chromosome 17q encoding for SkM1, the alpha-subunit of the sodium channel (Fontaine 1990; Fontaine 1997). The prevalence is estimated at 0.35 per 100,000 (Vivekanandam 2023). Both parayotonia congenita and sodium channel myotonia are generally inherited in a dominant manner, though some people have de novo variants.

In paramyotonia congenita, myotonia has a preponderance for affecting facial muscles, including eyelids and jaw muscles. People are often particularly sensitive to cold as a trigger for myotonia. The myotonia worsens after repetitive contractions (paradoxical myotonia). More recently, a more extensive sodium channel myotonia phenotype has been described and this includes childhood-onset myopathies and laryngospasm as part of the disease spectrum (Vivekanandam 2020b). We have included only classical paramyotonia and sodium channel myotonia in this review.

Pathophysiology

The pathophysiological mechanisms in the various myotonic disorders are different. In myotonic dystrophy type 1, the expanded CTG-repeat in myotonic dystrophy triggers aberrant splicing of chloride channel messenger ribonucleic acid (Charlet 2002; Mankodi 2002), but it is also possible that the myocytes in myotonic dystrophy display an abnormal sodium channel activity (Bernareggi 2005). Thus, the exact pathophysiological mechanism leading to myotonia in myotonic dystrophy is unknown. It could be assumed that there is an overlap with the non-dystrophic channelopathies.

The chloride channel myotonias are caused by a permanent reduction of the resting chloride conductance of the muscle fibre membranes (Franke 1991; Lipicky 1979). Normal chloride conductance is necessary for a fast repolarisation of the muscle fibre membranes, otherwise these tend to stay depolarised, causing myotonia (Jurkat-Rott 2001), or become hyperdepolarised, causing a loss of excitability of the muscle fibre membrane and thereby a transient paresis.

Sodium channel myotonias are caused by a long-lasting depolarisation of the muscle fibre membrane due to an inactivation defect of the sodium channels (Lehmann-Horn 1987a; Lehmann-Horn 1987b). These can initiate successive action potentials, which is the basis for myotonia (Jurkat-Rott 2001).

Description of the intervention

There is currently no cure for inherited myotonic disorders, so treatment is symptomatic. Theoretically, drugs that block the sodium channels, independent of the disease process involved, can diminish myotonia. These agents reduce the excitability of the cell membrane of skeletal muscle and include local anaesthetics, cardiac agents, such as anti-arrhythmic drugs, and anti-epileptic drugs.

The first treatment for myotonia was published by Wolf in 1936 who treated four people with myotonia congenita with quinine, an anti-arrhythmic drug (Wolf 1936). The literature also suggests that procainamide, tocainide, and phenytoin have favourable effects (Dengler 1979; Kwiecinski 1992; Leyburn 1959; Munsat 1967; Rüdel 1980; Streib 1986). However, procainamide and tocainide can have serious long-term adverse effects. Mexiletine was suggested as the agent of first choice in the mid-1990s (Rüdel 1994), but the published evidence basis for this opinion was unclear. There were some case reports (Ceccarelli 1992; Leheup 1986; Pouget 1983), one study with a heterogeneous population (Kwiecinski 1992), and an electrophysiological evaluation (Rossi 1985) on the use of mexiletine in people with myotonia. Other sodium channel active agents have been used over time, including flecainide showing improvement in myotonia (Desaphy 2013; Terracciano 2018). Case series have additionally described improvement of stiffness and function with flecainide treatment in particularly resistant or non-responsive people with myotonia (Desaphy 2013; Rosenfeld 1997). Acetazolamide is a carbonic anhydrase inhibitor traditionally thought of as a diuretic, but it has been described as useful for myotonia (Griggs 1978; Markhorst 2014; Ptácek 1994). Acetazolamide has been described to reduce both stiffness and pain (Markhorst 2014).

How the intervention might work

Drugs that block sodium channels (e.g. mexiletine and lamotrigine) are used for the treatment of myotonia. Mexiletine works by enhancing fast inactivation of sodium channels, reducing depolarisation. The effect is use-dependent. Lamotrigine works by shifting the voltage-gated dependence of inactivation to more negative potentials and has a slower onset and offset of action. Other sodium channel blockers such as ranolazine, which works on slow inactivation, have not been included in this review as trials are not randomised and are still explorative or in pilot stages.

Other drugs which have been used for the treatment of myotonia include clomipramine, imipramine, taurine, nifedipine, diazepam, and prednisone. It is hypothesised that the tricyclic antidepressants (imipramine and clomipramine) act on the sympathetic nerve terminals to increase levels of noradrenaline, which exerts an inhibitory influence on skeletal muscle membranes by β_2-adrenoreceptor stimulation (Bowman 1981; Gascon 1989). More recent work suggests that tricyclic antidepressants may also work by inhibiting skeletal muscle sodium channels in myotonia (Bourin 2009). Taurine, an amino-acid, may affect cellular hyperexcitability by increasing membrane conductance of potassium and chloride (Durelli 1982; Durelli 1983). All these types of drugs seem to act as membrane stabilisers. The mechanism of action of acetazolamide is not fully elucidated, but also thought to stabilise the muscle membrane through effects on other ion channels such as chloride and potassium (Markhorst 2014).

Why it is important to do this review

This is an update of a review first published in 2005 and previously updated in 2006, 2007, and 2010. Non-systematic reviews of therapy for the myotonic disorders have been published (Altamura 2023; Camerino 2008; Cleland 2008; Meola 2000; Meola 2004). One systematic review examined therapies in muscle channelopathies in non-dystrophic myotonia, also considering all levels of evidence and preclinical aspects (Desaphy 2021). This review extends to all myotonia, including both non-dystrophic myotonia and myotonic dystrophy, and focused on randomised controlled trials (RCT).

A crucial aspect to this review is how to quantify myotonia; a difficulty highlighted by a report of an experimental protocol to quantify myotonia using quantitative muscle assessment (Sansone 2000). Challenges include the variability of the myotonia between patients and within a given patient, at different times of the day and how to take account of the warm-up phenomenon. All these issues exacerbate the usual problem of inter-rater variability. Possible solutions might be the use of specific devices such as a dynamometer with a computerised protocol and cross-over trial designs (Logigian 2004; Logigian 2005).

One of the most used parameters of myotonia is the relaxation time after maximum voluntary contraction as measured by stopwatch, equipment such as a dynamometer, or computerised protocols. A related measure is the electromyographic variant, the electromyographic relaxation time after maximum voluntary contraction. Another parameter is the presence or absence of percussion myotonia. These parameters measure the impairment, but not the functional effect of myotonia. One functional test, the stair test (time needed to climb 10 stairs), is imprecise and also variable.

Patient-reported outcomes have the benefit of being clinically relevant and meaningful. Two patient-reported scores – the Interactive Voice Response Diary and the Myotonia Behaviour Score – have been developed and tested in a cohort of people with non-dystrophic myotonia (Hammaren 2005; Statland 2011). These two scores are the only two measures that have been specifically tested for utility and responsiveness in this specific cohort prior to being utilised in clinical trials and are likely to be the best measures to use.

This systematic review aimed to provide the evidence on which to base treatment. Understanding the evidence base to guide clinicians on treatment options for myotonia is crucial.

OBJECTIVES

To review evidence from randomised controlled trials (RCTs) on the efficacy and tolerability of drug treatment in people with clinical myotonia due to myotonic disorders.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised (alternate or other systematic treatment allocation) trials of any drug treatment in people with clinical myotonia due to one of the myotonic disorders described below where effect on myotonia is an outcome.

Types of participants

Participants of all ages with clinical myotonia caused by myotonic disorders including myotonic dystrophy and non-dystrophic myotonias. We presented results separately for myotonic dystrophy and non-dystrophic myotonias, where possible.

We excluded people with Hoffman's disease (myotonia in hypothyroidism), McArdle's disease, Brody's disease (sarcoplasmic reticulum-Ca^{2+}ATPase deficiency), neuromyotonic diseases, neuroleptic malignant syndromes, tetanus, and Schwartz-Jampel syndrome. For trials or treatment groups including people with myotonic dystrophy and non-dystrophic myotonias, we described the different diseases and the degree of myotonia separately, if this was possible.

Types of interventions

Any drug treatment (given either singly or in combination for at least two weeks) versus no therapy, placebo, or another active drug treatment. The list of potential drugs included quinine, procainamide, tocainide, phenytoin, mexiletine, lamotrigine, and acetazolamide, but this list was not exclusive.

Types of outcome measures

Primary outcomes

- **Improvement in clinical myotonia** as measured by validated participant-reported outcome measures, such as the Interactive Voice Response score and the Myotonia Behaviour Score.

Secondary outcomes

- **Relaxation time:** the time taken to fully open the hand or eyelid after a maximum voluntary contraction (hand-grip myotonia). This might be determined manually by stopwatch or by computerised protocols. When using a computerised hand-grip myometer, the decline in maximum voluntary contraction from 90% to 5% during relaxation is frequently used to measure the relaxation time. However, some researchers have used 50%, 75%, or 100% decline from peak maximum voluntary contraction as the relaxation time. We included all such protocols.
- **Electromyographic relaxation time:** the phenomenon of myotonia can be recorded with an electromyographic needle electrode and are seen as positive waves, so-called myotonic discharges or after-discharges. After maximum voluntary contraction, these myotonic or after-discharges wax and wane and finally stop. The duration of these after-discharges is also called electromyographic relaxation time. For example, after-discharges can be recorded from the opponens pollicis muscle.
- **Occurrence of one or more adverse events during treatment with the different agents:** an adverse event is any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship.
- **Quality of life:** the 36-item Short Form (SF-36) measures eight scales including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. It is a validated score rated from 0 to 100 where lower scores equate to more disability. Quality of life was also measured using IN QOL which is also a validated health questionnaire consisting of 45 items within 11 subscales looking at symptoms, life domains, and treatment effects. Items are scored on a 7-point scale from 0 to 6 or from 1 to 7 and a higher total score indicated higher disability.

For all outcome measures, we used a minimum treatment duration of one week and maximum treatment duration of 12 weeks and, where necessary, planned to adjust for different follow-up periods.

Search methods for identification of studies

Electronic searches

We searched the following databases on 29 March 2023.

- Cochrane Neuromuscular Specialised Register via CRS Web (to 29 March 2023; Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL) via CRS Web (2023, Issue 3; Appendix 2)
- MEDLINE(R) ALL Ovid (1946 to 28 March 2023; Appendix 3)
- Embase via OvidSP (1974 to 2023 week 12; Appendix 4)
- ClinicalTrials.gov (https://clinicaltrials.gov; 29 March 2023; Appendix 5)
- World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int; 29 March 2023; Appendix 6)

There were no language, publication date, document type, or publication status limitations for this search.

Searching other resources

We handsearched grey literature such as neuromuscular textbooks (*Myology* (Lehmann-Horn 1994; Rüdel 1994)) and abstracts from international neuromuscular congresses (World Muscle Society/ American Academy of Neurology (WMS/AAN)), and we checked the reference lists of the identified literature and reviews concerning myotonia. We also contacted authors, disease experts, and manufacturers of antimyotonic drugs.

Data collection and analysis

Selection of studies

Two review authors (from JT, CG, JS, GD, and VV) independently reviewed the titles and abstracts from the electronic search to identify relevant trials for full review. We obtained the full text of all potentially relevant studies for assessment. The review authors decided which trials met the inclusion criteria. We resolved

disagreements by discussion. Review authors were not blinded to trial authors' names, institutions, and the journals of publication.

We excluded studies that were not randomised or did not include an assessment of clinical myotonia. We excluded studies that assessed mobility, myopathy, or disease progression, and did not assess myotonia independently. This was agreed by all review authors. We listed studies ongoing at the time of analysis in the Ongoing studies section of the review for consideration in future updates of the review.

Data extraction and management

Five review authors (JT, CGF, JS, GD, and VV) independently performed data extraction on participants, methods, intervention, and outcomes using a data extraction form. We contacted authors of the new included studies to request any missing data during data extraction. We combined studies performed on the same cohort of participants (e.g. non-dystrophic myotonia) and using the same outcome measure in forest plots where appropriate. All other outcomes measures are presented descriptively.

Assessment of risk of bias in included studies

Two review authors (from JT, CG, JS, GD, and VV) independently assessed the risk of bias in the included trials with respect to the following items: random sequence generation, allocation concealment, participant blinding, observer blinding, incomplete outcome data, selective reporting, and other sources of bias such as explicit diagnostic inclusion and exclusion criteria. We also assessed the overall risk of bias. We assessed these items using the Cochrane RoB 1 tool according to the *Cochrane Handbook for Systematic Reviews of Interventions* as at high, low, or unclear risk of bias (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (one of JT, CG, JS, GD, and VV).

Measures of treatment effect

We planned to analyse the primary outcome, improvement in participant-reported clinical myotonia, and secondary outcome, occurrence of adverse events, as dichotomous data and present them as odds ratios with 95% confidence intervals (CIs), where possible. However, included trials reported the primary outcome in a range of formats, mostly as continuous outcomes; therefore, we reported results for improvement in participant-reported clinical myotonia according to the scales used in the included trials.

We analysed secondary outcomes (relaxation time, electromyographic relaxation time, and quality of life measures) as continuous data with mean difference (MD) and 95% CIs.

Where suitable outcome data were not available to report measures of treatment effect, and due to the cross-over design of many included studies, we presented outcome data descriptively.

Unit of analysis issues

For trials with a cross-over design, we made an assessment of the likelihood of a carry-over effect (i.e. the treatment effects of the first treatment period carrying over into the second treatment period) by examining lengths of washout periods (if used) and if trials reported any investigations of possible carry-over effect.

Where we judged the risk of carry-over effect to be low, we planned to analyse data from trials of a cross-over design using approaches recommended by Elbourne 2002; preferably extracting and analysing data from paired analyses where possible, or by extracting and analysing data from the first period of the trial (prior to cross-over) as an alternative approach.

For our primary outcome, if all necessary data could have been deduced from the published results and published as dichotomous data, we planned to analyse the primary outcome for cross-over studies using the McNemar's test (Armitage 1987; Breslow 1980), calculating the odds ratios.

If we were concerned about the risk of a carry-over effect in a cross-over trial (e.g. if the trial did not employ a washout period or if statistical testing within the trial indicated that carry-over had occurred), we reported only first-period data from that trial (or made a narrative summary of results from the trial if first-period data were not available).

Dealing with missing data

We attempted to obtain missing data from the trial authors if this was necessary. We used an intention-to-treat approach for analysis in this review (i.e. analysis according to allocated treatment groups, irrespective of compliance or loss to follow-up), as far as possible.

Assessment of heterogeneity

We intended to assess clinical heterogeneity by reviewing the differences across trials in the characteristics of recruited participants and treatment protocols. We assessed statistical heterogeneity using a Chi^2 test. We assessed heterogeneity using the Q test ($P < 0.10$ for significance) and the I^2 statistic (greater than 50% indicating considerable heterogeneity; Higgins 2003), and visually by inspecting forest plots.

Assessment of reporting biases

We made a full attempt at identifying unpublished trials and aimed to minimise any potential publication bias using a comprehensive, systematic search strategy.

We were unable to formally assess publication bias among the studies as there were fewer than 10 studies for each comparison. In future updates, if additional studies are identified, we will examine funnel plots for asymmetry as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

For the included trials, we made an assessment of outcome reporting bias by comparing the methods section of the full text to the results section to determine if all outcomes that were measured were reported.

Data synthesis

Where more than one trial compared the same intervention and control for the same outcome, we intended to perform meta-analysis and calculate a pooled treatment effect across those trials using a fixed-effect model presented as forest plots. We interpreted a P value of 0.05 or less as statistically significant. If there was clinical heterogeneity or considerable statistical heterogeneity (e.g. I^2 statistic greater than 50%) in analyses which could not be readily explained, we would have presented results using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If there was clinical heterogeneity or considerable statistical heterogeneity (e.g. I^2 statistic greater than 50%) in analyses, we intended to examine differences in trial design and participant characteristics and perform subgroup or sensitivity analyses if necessary to explore plausible causes. If heterogeneity could still not be explained, we would have reported the results using a random-effects model.

We would have analysed myotonic dystrophy and non-dystrophic myotonias as subgroups if possible, but data presented in included trials did not allow for this subgroup analysis.

Sensitivity analysis

If there was clinical heterogeneity or considerable statistical heterogeneity (e.g. I^2 statistic greater than 50%) in analyses, we intended to examine differences in trial design and participant characteristics and perform subgroup or sensitivity analyses if necessary to explore plausible causes. Furthermore, if we had concerns about the methodological quality of any included studies (high risk of bias for more than one domain of the Cochrane RoB 1 tool, see Assessment of risk of bias in included studies), we would have performed sensitivity analyses excluding the studies at high risk of bias and comparing results of sensitivity analyses to original analyses to examine robustness of results.

Summary of findings and assessment of the certainty of the evidence

We presented all outcomes in summary of findings tables for the comparisons of mexiletine versus placebo and lamotrigine versus placebo. These treatments had the largest, most recent studies and are the primary treatment choices used by specialist clinicians in the field.

We presented separate summary of findings tables for myotonic dystrophy type 1 (Summary of findings 1), and non-dystrophic myotonias (Summary of findings 2 and Summary of findings 3).

Three review authors (VV, SN, JS) assessed the certainty of the evidence as 'high,' 'moderate,' 'low,' or 'very low' using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the body of evidence. We used methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

We reported decisions to downgrade the certainty of evidence in the footnotes of the summary of findings tables and in the results section for each outcome. For comparisons that were not included in the summary of findings tables, available results are summarised in Table 1, Table 2, and Table 3, and the certainty of evidence was reported in the Effects of interventions section.

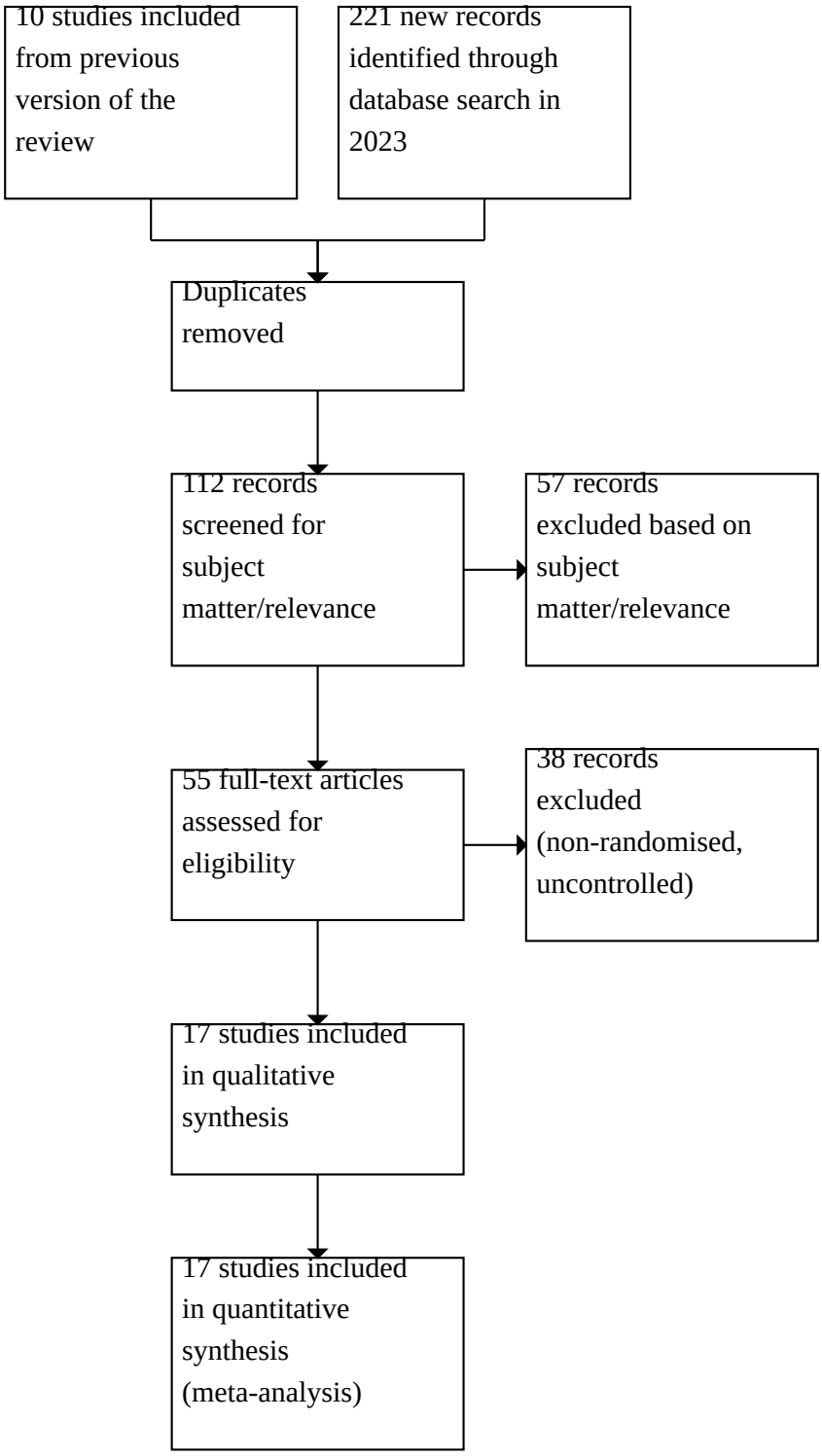
RESULTS

Description of studies

Results of the search

The latest electronic search conducted in March 2023 identified 221 records and 10 records from the original review. After removal of duplicates and clearly irrelevant records, we screened 112 abstracts and titles and discarded 57 records. We screened the full text of the remaining records and excluded 38 records. We included 17 eligible studies (see Figure 1). See Characteristics of included studies and Characteristics of excluded studies tables. The cross-over trials of Logigian 2010a and Logigian 2010b used mexiletine at dosages of 150 mg three times daily and 200 mg twice daily in people with myotonic dystrophy type 1 – this was one study but we separated the dosages in the review for analysis. No studies are awaiting classification and we identified five ongoing studies (see Characteristics of ongoing studies table).

Figure 1. Study flow diagram, illustrating the study selection process. The strategies have been refined several times and earlier results predate requirements for PRISMA search totals.



Included studies

See Characteristics of included studies table.

The original Cochrane search revealed 10 trials that compared active drug treatment with placebo for the treatment of myotonia in 143 participants (113 participants with myotonic dystrophy and 30 participants with non-dystrophic myotonia) (Antonini 1990; Durelli 1983; Finlay 1982; Gascon 1989; Grant 1987; Kratz 1986; Kwiecinski 1992; Lewis 1966; Leyburn 1959; Munsat 1967). One of these trials compared two different drug treatments for the treatment of myotonia in 10 participants with myotonic dystrophy type 1 (Finlay 1982).

This update included a further seven trials in people with myotonic dystrophy or non-dystrophic myotonia (249 participants; 106 with myotonia dystrophy and 143 with non-dystrophic myotonia; Andersen 2017; Bassez 2018; Heatwole 2021; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018; Vicart 2021 (Logigian 2010a and Logigian 2010b are one study that used two dosages so appeared twice in this list)). Therefore, this update included 17 trials with 392 participants (219 with myotonic dystrophy type 1 and 173 with non-dystrophic myotonia; Table 1). Studies were randomised and single-blind or double-blind with treatment periods ranging from two weeks to 12 months.

Trial design

Thirteen were cross-over studies. Three were parallel group, randomised, placebo-controlled studies. One was an aggregated n-of-1 study (Stunnenberg 2018). Kwiecinski 1992 started as a cross-over study and afterwards, randomised participants to three different study drugs. The sum of the number of participants in the different treatment groups in the randomised part of the study exceeded the total number of included participants. An attempt to clarify this with the author was unsuccessful. We assumed the second part of the study was not randomised until we receive evidence to the contrary. Most studies were double-blind, and two studies were single-blind (Grant 1987; Kwiecinski 1992). The trial durations and washout periods are described in Table 1.

Participants

Most trials described did not provide baseline characteristics of the individual participants or of the two separate groups. Five trials gave no baseline characteristics (Durelli 1983; Kratz 1986; Lewis 1966; Leyburn 1959; Munsat 1967). Three trials described the individual groups well (Andersen 2017; Bassez 2018; Statland 2012), whereas the other trials gave the characteristics of the entire study population. While most trials defined a cohort of either people with non-dystrophic myotonia or myotonic dystrophy, five trials had a mixed population of people with non-dystrophic myotonia and myotonic dystrophy (Kratz 1986; Kwiecinski 1992; Lewis 1966; Leyburn 1959; Munsat 1967). Five trials did not define explicit inclusion criteria (Finlay 1982; Gascon 1989; Kratz 1986; Lewis 1966; Leyburn 1959). Six trials defined explicit exclusion criteria (Andersen 2017; Antonini 1990; Bassez 2018; Logigian 2010a; Logigian 2010b; Statland 2012). One trial excluded people with cardiac, ophthalmological, or urological diseases (Antonini 1990). Since cardiac and ophthalmological symptoms are features of myotonic dystrophy, this trial probably included a selected group of patients.

Interventions

The regimens of treatment varied between studies (see Characteristics of included studies table and Table 1). Most studies used drugs that block sodium channels (e.g. mexiletine and lamotrigine). Other drugs used were clomipramine, metformin, imipramine, nifedipine, taurine, procainamide, disopyramide, quinine, phenytoin, tocainide, diphenylhydantoin, diazepam, and prednisone.

Outcome measures

The outcome measures used differed vastly between trials. Even for the same outcome – grip myotonia relaxation time – the method for undertaking this differed between trials. Some studies used a mean of three repetitions, some used grip around two fingers, and some used computer-based assessments determining peak force. A few studies used electromyographic and surface electromyographic but the methodology differed even between the use of electromyography. A few studies used the Six-Minute Walk Test, which has been validated in other muscle conditions for weakness or myopathy but not for myotonia in non-dystrophic myotonia and myotonic dystrophy type 1. One of the key limitations of the Six-Minute Walk Test in myotonia is the difficulty to account for warm-up or paradoxical myotonia phenomenon. Additionally, while gait and axial stiffness is a major issue for people with chloride channel myotonia, for people with sodium channel myotonia, face and jaw stiffness are prominent and cannot be accounted for by the Six-Minute Walk test. Grip and electromyographic outcomes in non-dystrophic myotonia and dystrophic myotonia are not yet longitudinally validated.

Our primary outcome measure was participant-reported myotonia. Validated outcome measures to date include the Interactive Voice Response score and the Myotonia Behaviour Score. Both are participant-reported outcomes. The Interactive Voice Response score is a 1 to 9 severity scale and the Myotonia Behaviour Score is 0 to 5 where sentences describing the impairment correspond to numbers. The Visual Analogue Scale has been validated for use in other conditions such as pain syndromes; however, it has not been validated in non-dystrophic myotonia or dystrophic myotonia.

The outcome measures used differed vastly between trials, as described in Table 1. The most frequently used outcome measure was the grip myotonia relaxation time in seconds. It was measured after three seconds (Antonini 1990; Logigian 2010a; Logigian 2010b), two to three seconds (Gascon 1989), five seconds (Lewis 1966), and three minutes (Finlay 1982) of maximum voluntary contraction. Other studies did not specify the length of maximum voluntary contraction (Grant 1987; Kratz 1986; Kwiecinski 1992). Logigian 2010a and Logigian 2010b used a computerised protocol to measure relaxation times after a maximal voluntary isometric contraction. Each session consisted of six maximal voluntary contractions, each lasting three seconds, with a 10-second rest period between each contraction. Three sets of measurements (repetitions) were performed with 10-minute intervals of rest between repetitions. An automated computer program first determined peak force in kilogram units and then placed cursors on the declining, relaxation phase of the force recording at various levels of peak force: 90%, 50%, and 5%. The relaxation times reported in this paper are the times required for decline in force from 90% to 5%, 90% to 10%, and 50% to % of peak force.

Statland 2012 assessed eyelid and hand grip myotonia after five seconds of hand grip squeeze and eyelid closure. Five repetitions of each manoeuvre were performed and the time to open was recorded on a stopwatch. This study also used a quantitative measure of handgrip myotonia using a grip dynamometer and computerised capture system. The maximum voluntary contraction following forced right-hand grip and the time to relax from 90% to 5% were recorded using automated analysis software. Andersen 2017 recorded relaxation time after five seconds of maximal voluntary contraction of handgrip and eyelid closure. Five repetitions were performed to identify warm-up phenomenon. Bassez 2018 recorded handgrip relaxation using a dynamometer.

Three studies used electromyographic relaxation times (after-discharges) in seconds after maximum voluntary contraction (Durelli 1983; Kratz 1986; Kwiecinski 1992). Additional ways of measuring relaxation time were used, such as electromyographic surface electrodes (Lewis 1966), or an ergographic device (Munsat 1967). Two trials used a mean score of three relaxation times (Gascon 1989; Lewis 1966), and one trial used a mean score of five relaxation times after maximum voluntary contraction (Grant 1987). Another trial used a mean score of six measurements consisting of three clinical relaxation times and three electromyographic relaxation times (Leyburn 1959). Electromyographic myotonia was graded on a 1+ to 3+ scale (Statland 2012).

Other outcome measurements were occurrence of percussion myotonia (Durelli 1983), percussion myotonia in seconds (Gascon 1989), lid myotonia in seconds after firm closure (Kwiecinski 1992), occurrence of myotonic discharge induced by electrical stimulation of the median nerve (Durelli 1983), potassium chloride loading test in millimoles per litre for occurrence of myotonia (Durelli 1983), time to climb 10 stairs (stair test) (Kwiecinski 1992), and subjective responses (Finlay 1982; Kwiecinski 1992), and maximal postexercise decrement in compound muscle action potential after short and long exercise tests (Statland 2012).

Three studies assessed quality of life studies using the SF-36 or Individualized Quality of Life (INQoL) (Andersen 2017; Bassez 2018; Statland 2012).

Analysis populations

Most trials were analysed on a per-protocol basis instead of an intention-to-treat basis (withdrawals were not included in the analysis). Nine trials were at low risk of bias as they used an intention-to-treat or modified intention-to-treat analysis, and clearly reported withdrawals and losses to follow-up (Andersen 2017; Durelli 1983; Grant 1987; Heatwole 2021; Kratz 1986; Logigian 2010a; Logigian 2010b; Munsat 1967; Vicart 2021). Two trials were at low risk of bias as they did not clearly report withdrawals and losses to follow-up and how these were handled in analyses (Bassez 2018; Statland 2012).

Excluded studies

See Characteristics of excluded studies table.

We excluded 38 studies. Four studies were new to this update. Arnold 2017 was a non-randomised pilot study. Chisari 2009 was a non-randomised study with no control group. Heatwole 2011 was not randomised and did not have a myotonia outcome measure. Lorusso 2019 was an open-label study and was not randomised.

In the previous version of this review, 17 were non-randomised or uncontrolled studies (Backman 1990; Birnberger 1975; Brumback 1983; Durelli 1982; Griggs 1977; Griggs 1978; Guilleminault 1978; Matsumura 2004; Mielke 1985; Milner-Brown 1990; Müller 1980; Orndahl 1986; Ricker 1980; Rüdel 1980; Samaha 1964; Sechi 1983; Sugino 1998), and 10 were case studies (Alfonsi 2007; Benstead 1987; Cook 1984; Garai 1954; Geschwind 1955; Hughes 1991; Jackson 1994; Karli 1974; Pendefunda 1974; Streib 1987).

We excluded studies focusing on strength in myotonic dystrophy (e.g. Griggs 1989; Orndahl 1994). A further five studies did not have independent measures of myotonia (Pénisson-Besnier 2008; Schneider-Gold 2003; Tarnopolsky 2004; Vlachopapadopoulou 1995; Walter 2002).

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

See Characteristics of ongoing studies table.

The following studies are ongoing or awaiting publication.

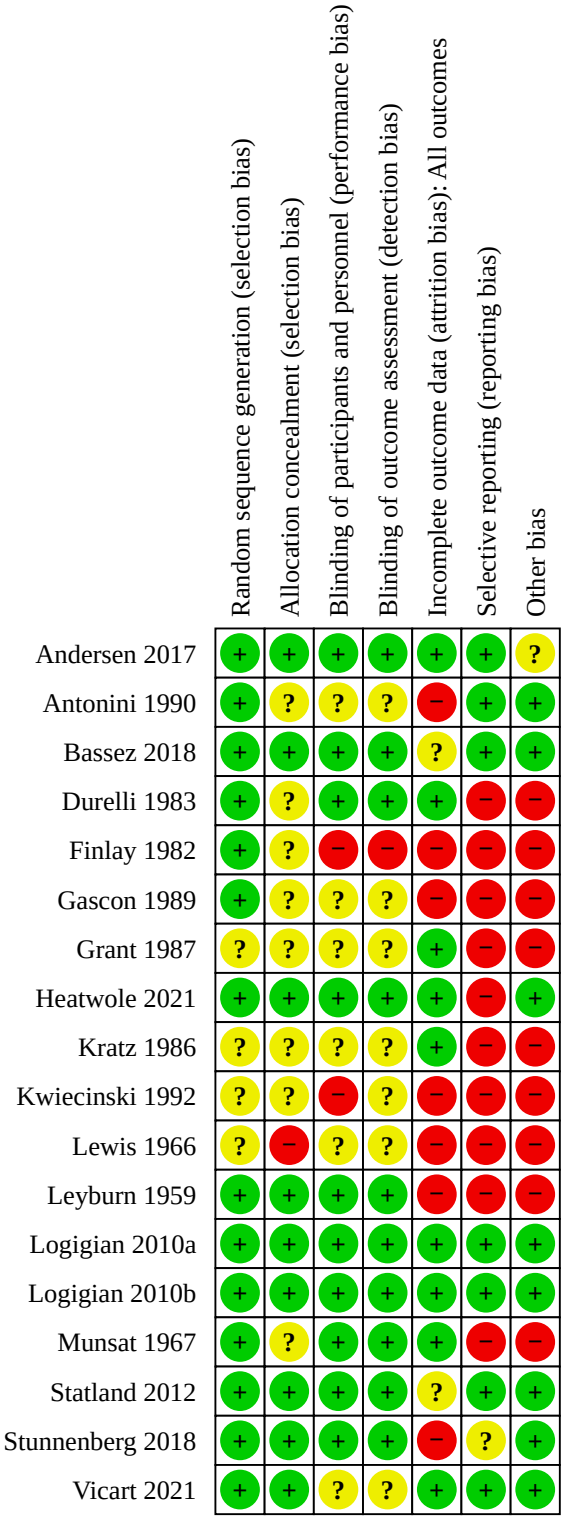
- MEND: MExiletine versus lamotrigine in Non-Dystrophic myotonia (NCT05017155)
- Open-label extension study in paediatric patients who have completed the MEX-NM-301 study (NCT04622553)
- Open label study in adolescents and children with myotonic disorders (NCT04624750)
- Safety and efficacy of tideglusib in congenital myotonic dystrophy (REACH CDM) (NCT03692312)
- Treatment of myotonia – lamotrigine versus namuscla (NCT05639257).

Since the search date and initial submission of this review, MEND: MExiletine versus lamotrigine in Non-Dystrophic myotonia has been published (Vivekanandam 2024). The study findings supported the conclusions of this review of the utility of mexiletine and lamotrigine for symptomatic treatment of myotonia. Subsequent updates of this review will incorporate this and further completed studies.

Risk of bias in included studies

See Figure 2 for a summary of review authors' judgements about each risk of bias item for each included study. In general, the trials were small, with the participant numbers ranging from nine to 59 (Statland 2012 had 59, Bassez 2018 had 40), and risk of bias was high.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Allocation concealment was unclear in eight studies (Antonini 1990; Durelli 1983; Finlay 1982; Gascon 1989; Grant 1987; Kratz 1986; Kwiecinski 1992; Munsat 1967). For Lewis 1966, allocation concealment was inadequate; the procedure was described as "arbitrary by secretary," and the study was at high risk of bias. The remaining eight studies described an adequate method of randomisation and allocation concealment and the risk of selection bias was low (Andersen 2017; Bassez 2018; Heatwole 2021; Leyburn 1959; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018; Vicart 2021).

Blinding

In nine trials, blinding of participants, personnel, and outcome assessors was adequate and they were at low risk of bias (Andersen 2017; Bassez 2018; Durelli 1983; Heatwole 2021; Leyburn 1959; Logigian 2010a; Logigian 2010b; Munsat 1967; Statland 2012; Stunnenberg 2018). In six trials, the blinding was unclear because it was not described (Antonini 1990; Gascon 1989; Grant 1987; Kratz 1986; Lewis 1966; Vicart 2021). In two trials, the risk of performance or detection bias was high. In Finlay 1982, participant blinding was inadequate because participants could recognise the adverse effects having used the medication previously in a clinical setting and this was not accounted for. Kwiecinski 1992 was a single-blind trial without blinding of personnel (unclear if outcome assessors were blinded). None of the trials recorded effectiveness of blinding.

Incomplete outcome data

Seven trials were at high risk of bias as they were analysed on a per-protocol basis instead of an intention-to-treat basis and withdrawals were not included in the analysis (Antonini 1990; Finlay 1982; Gascon 1989; Kwiecinski 1992; Lewis 1966; Leyburn 1959; Stunnenberg 2018). The remaining trials used an intention-to-treat or modified intention-to-treat analysis and clearly reported withdrawals and losses to follow-up and were at low risk of bias (Andersen 2017; Durelli 1983; Grant 1987; Heatwole 2021; Kratz 1986; Logigian 2010a; Logigian 2010b; Munsat 1967; Vicart 2021), but two trials did not clearly report withdrawals and losses to follow-up and how these were handled in analyses (Bassez 2018; Statland 2012).

Selective reporting

Six studies clearly reported results for all primary and secondary outcomes listed in the methods section and were at low risk of bias (Andersen 2017; Antonini 1990; Bassez 2018; Logigian 2010a; Logigian 2010b; Statland 2012; Vicart 2021). One study clearly reported primary outcomes but not all secondary outcomes, so the risk of selective reporting bias was unclear (Stunnenberg 2018). The remaining 10 trials were at high risk of selective reporting; results of treatment periods from cross-over studies were not reported (Durelli 1983; Gascon 1989; Grant 1987; Lewis 1966; Leyburn 1959; Munsat 1967); results for participants in the placebo group were not reported (Heatwole 2021); results for secondary outcome measures including hand grip myotonia for three participants in the placebo group were not reported or clearly accounted for; not all outcomes were measured for all participants (Kwiecinski 1992); and there were only limited descriptive results with no statistical analysis (Finlay 1982; Kratz 1986). Attempts to contact the trial authors to request results which were not reported were unsuccessful.

Other potential sources of bias

Eight studies were of cross-over design without washout intervals and were at high risk of other bias (Durelli 1983, testing taurine; Finlay 1982, testing disopyramide and procainamide; Gascon 1989, testing imipramine; Grant 1987, testing nifedipine; Kratz 1986, testing mexiletine, Kwiecinski 1992, testing disopyramide, phenytoin, mexiletine, and tocainide; Leyburn 1959, testing quinine, prednisone, and procainamide; and Munsat 1967, testing diphenylhydantoin and procainamide).

Since a washout interval was not incorporated, there is a strong possibility of a carry-over effect (bias) and data from the first treatment arms (prior to cross-over) were not presented for any of these studies; data were inappropriately presented in the form of combined results of both active treatment arms and both placebo arms. Furthermore, three of these studies included participants with myotonic dystrophy and participants with myotonia congenita, without defining subgroups. We tried to contact the authors of the trials but have not yet been successful in obtaining the raw data. For these reasons, due to the likely bias from a carryover effect, we presented only a narrative summary of the results for our specified outcomes from these trials if reported.

One trial was at high risk of bias and had a large placebo effect (Lewis 1966). Research into the placebo tablets identified that they contained quinine sulphate 0.5 mg per tablet. This substance could be an active treatment for myotonia, resulting in bias.

One trial calculated an initial sample size of 42 participants and was at unclear risk of other bias (Andersen 2017). However, after interim analysis with defined stopping criteria, the study was stopped at 26 participants. It is unclear whether the study was powered to detect differences based on the sample size recruited.

The remaining studies had no other sources of bias (Antonini 1990; Bassez 2018; Heatwole 2021; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018; Vicart 2021).

Effects of interventions

See: **Summary of findings 1** Mexiletine compared to placebo for myotonic dystrophy type 1; **Summary of findings 2** Mexiletine compared to placebo for non-dystropic myotonias; **Summary of findings 3** Lamotrigine compared to placebo for non-dystropic myotonias

Mexiletine versus placebo

Summary of trials

Eight trials compared mexiletine to placebo (Heatwole 2021; Kratz 1986; Kwiecinski 1992; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018; Vicart 2021).

Kratz 1986 recruited six participants with both myotonic dystrophy type 1 and non-dystrophic myotonia. There was limited information available for this study and no useable results. It was a double-blind cross-over study. However, further details, such as methods of randomisation, blinding, and inclusion/exclusion criteria, were not reported. This is an old study at high risk of bias with small numbers of a heterogeneous cohort.

Kwiecinski 1992 had nine people with myotonic dystrophy type 1 and 21 people with non-dystrophic myotonia. There was no

washout period. Therefore, there is a strong possibility of a carry-over effect. While inclusion criteria were defined, other aspects, such as method of randomisation, were not described. This was a single-blind, placebo-controlled study where the study observers/examiners were not blinded, increasing risk of bias. Two participants dropped out and outcome data for this trial were incomplete as not all participants were measured for all outcomes. This trial had substantial bias.

The cross-over trials, Logigian 2010a and Logigian 2010b, used mexiletine at dosages of 150 mg three times daily and 200 mg twice daily in people with myotonic dystrophy type 1. Treatment periods were seven weeks, separated by a four- to eight-week washout period. Each trial recruited 20 participants, but 10 participants were enroled in both trials; therefore, meta-analysis of the results of these trials was not possible. The studies were double-blind with clear inclusion and exclusion criteria, and randomisation was described. Two participants in each trial withdrew from the study. Only participants who completed the study were included in the analysis. While the risk of bias was low, the numbers of participants were small.

Statland 2012 recruited 59 people with non-dystrophic myotonia to this cross-over study comparing placebo and mexiletine 200 mg three times daily. The study was double-blind with procedures for blinding, randomisation, and allocation concealment. Inclusion and exclusion criteria were well described. Two participants dropped out of the trial but an intention-to-treat analysis was undertaken. Treatment effect analysis used the random-effects model. All participants completed the primary outcome, but not all secondary outcome measures were attained for all participants. Overall, the study was at low risk of bias and had a large number of participants for such a rare disease.

Heatwole 2021 recruited 41 people with myotonic dystrophy type 1 into a placebo-controlled trial comparing the effect of mexiletine 150 mg three times daily to placebo. While the initial inclusion and exclusion criteria were clearly defined, the inclusion criteria were modified during the study to allow more participants to be eligible. Participants were permitted to have a baseline six-minute walk distance greater than 500 m and not to have genetic confirmation of myotonic dystrophy type 1 if they had clinical symptoms of myotonic dystrophy type 1 and a first-degree relative with a positive genetic test. The study was double-blind, and randomisation and allocation procedures were clearly described. Participants underwent block randomisation. Data were analysed using an intention-to-treat analysis. Two participants dropped out of the study and were accounted for. Overall, the trial procedures were well described with a low risk of bias and a good sample size.

Vicart 2021 recruited 26 people with non-dystrophic myotonia into a cross-over study comparing mexiletine 600 mg total daily dose versus placebo with a four- to eight-day washout period. The number of participants was small and the method of sample size calculation was not clearly described. While the primary outcome was a participant-reported score, it was not validated in this group. Inclusion and exclusion criteria were clearly described; however, people were included if they had myotonia involving two segments of the body based on examiner assessment and three of seven areas of disability (talking, writing, feeding, hygiene, getting dressed, walking, and climbing stairs). This inclusion criterion was likely to create a select group of more severely affected participants and may not be generalisable. Randomisation was stratified according to diagnosis (myotonia congenita or paramyotonia congenita), and procedures for allocation concealment were clearly described. Analysis was performed using a modified intention-to-treat after assessing for and ruling out significant carryover effect. Four participants were not included in this analysis – only one had an adverse event. The study reported 40 distinct adverse events, but these were not fully detailed. There was a moderate risk of bias in this study with a small sample size.

Stunnenberg 2018 used a Bayesian trial design to investigate mexiletine 600 mg total daily dose in people with non-dystrophic myotonia. They combined 30 individual n-of-1 trials. Each individual trial consisted of 11 weeks with one to four treatment sets. A treatment set was considered four weeks of mexiletine and four weeks of placebo with a one-week washout in between. The sample size calculation was clearly described as were recruitment and clear inclusion and exclusion criteria. Randomisation was computer-based and methods were well described. A hierarchical Bayesian model was used for analysis. Overall, the study was at low risk of bias. While the sample size was small when considering traditional RCTs, using a validated outcome measure and adaptive trial designs powered the study sufficiently for this sample.

Mexiletine versus placebo in myotonic dystrophy type 1

See Summary of findings 1.

Primary outcome

Improvement in participant-reported clinical myotonia

No studies reported improvement in clinical myotonia using a validated participant-reported scale. Heatwole 2021 reported a Visual Analogue Scale treatment effect of −2.61 (95% CI −20.92 to 15.70; 42 participants; Analysis 1.1). Although the Visual Analogue Scale is a participant-reported scale, it is not validated in this patient cohort, so we are uncertain about the effect.

Secondary outcomes

Relaxation time

Two studies measured relaxation time (from 90% to 5%) (Heatwole 2021; Logigian 2010a (mexiletine 150 mg three times daily); Logigian 2010b (mexiletine 200 mg three times daily)). Logigian 2010a and Logigian 2010b used computerised protocols.

Mexiletine likely reduces hand grip relaxation time compared to placebo (mexiletine 150 mg 3 times daily: MD −1.37, 95% CI −1.86 to −0.87; I^2 = 0%; 2 studies, 56 participants; moderate-certainty evidence; Analysis 1.2; mexiletine 200 mg 3 times daily: MD −1.36, 95% CI −2.09 to −0.63; moderate-certainty evidence; 1 study, 18 participants; Analysis 1.2). We downgraded the certainty of the evidence for potential bias.

Electromyographic relaxation time

No studies reported electromyographic relaxation time.

Adverse events

Three studies reported adverse events (Heatwole 2021; Kwiecinski 1992 (adverse events reported together for myotonic dystrophy type 1 and non-dystrophic myotonia); Logigian 2010a; Logigian 2010b). Overall, there were 84 adverse events in the mexiletine group and 55 adverse events in the placebo group (Table 2; low-certainty evidence). We downgraded the certainty of the evidence

for risk of bias and imprecision. The most frequent adverse events with mexiletine were gastrointestinal symptoms, lethargy, and headache. While rare electrocardiograph changes and palpitations occurred, there were no serious cardiac events reported. Rates of specific adverse events were similar with mexiletine and placebo, where reported.

Quality of life

One study (38 participants) measured quality of life using the SF-36 PCS and MCS and the INQoL score (Heatwole 2021).

There may be no difference in quality of life between mexiletine and placebo on any scale (SF-36 PCS: MD −1.40, 95% CI −5.56 to 2.76; low-certainty evidence; Analysis 1.3; SF-36 MCS: MD −1.10, 95% CI −6.17 to 3.97; low-certainty evidence; Analysis 1.3; INQoL: MD 3.90, 95% CI −4.65 to 12.45; low-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence for all scores due to risk of bias and imprecision.

Mexiletine versus placebo in non-dystrophic myotonias

See Summary of findings 2.

Primary outcome

Improvement in participant-reported clinical myotonia

Two studies assessed participant-reported improvement in clinical myotonia using an Interactive Voice Response Diary, which is validated in people with non-dystrophic myotonia (Statland 2012; Stunnenberg 2018). Statland 2012 reported stiffness as the most common and most severe symptom of myotonia. Due to a potential carry-over effect in this analysis (P = 0.04 from Wald Test for carry-over), we presented results separately by treatment period. Stunnenberg 2018 presented results from both treatment periods, so there was no significant randomisation order or period effect. Due to the differences in the reporting of results (i.e. separately by treatment period or for both treatment periods combined), we did not pool the results of the two trials; we presented results by treatment period and overall in forest plots in Analysis 2.1.

Mexiletine likely reduces stiffness compared with placebo in both the first and second treatment period, and both treatment periods (first: MD −1.68, 95% CI −2.66 to −0.70; 1 RCT, 59 participants; second: MD −3.67, 95% CI −4.65 to −2.69; 1 RCT, 59 participants; both treatment periods: MD −3.12, 95% CI −3.75 to −2.49; 1 RCT, 30 participants; moderate-certainty evidence for all three). We downgraded the certainty of the evidence due to inconsistency.

Vicart 2021 reported within-group differences rather than between-group differences, limiting the incorporation of primary outcomes into our meta-analysis. Using the Visual Analogue Scale, there was a median change in stiffness of −78% compared to baseline for participants treated with mexiletine compared with a median change of +2% with placebo.

In Stunnenberg 2018, the mean treatment effect for Interactive Voice Response-reported pain was 0.68 (95% credible interval −0.52 to 1.89), for Interactive Voice Response-reported weakness was 1.48 (95% CI 0.18 to 2.77), and for tiredness was 1.23 (95% CI −0.23 to 2.67).

Secondary outcomes

Relaxation time

Two studies (89 participants) reported relaxation time using eye closure and clinical hand grip (seconds) (Statland 2012; Stunnenberg 2018). We pooled the results using a random-effects meta-analysis.

There is likely no effect on relaxation times with no differences in eye closure or clinical hand grip between mexiletine and placebo. There was substantial heterogeneity present in the analysis and CIs included advantages to both mexiletine and placebo (eye closure: MD −1.04, 95% CI −2.76 to 0.69; I^2 = 80%; clinical hand grip: MD −0.62, 95% CI −1.37 to 0.14; I^2 = 68%; both moderate-certainty evidence; Analysis 2.2). We downgraded the certainty of the evidence due to inconsistency.

Statland 2012 also reported quantitative hand grip (90% to 5%), which was improved with mexiletine compared to placebo (MD −0.11, 95% CI −0.18 to −0.04; Analysis 2.2).

Electromyographic relaxation time

Statland 2012 measured electromyographic relaxation time as right abductor digiti minimi and right tibialis anterior needle electromyographic. Stunnenberg 2018 measured myotonic discharges on needle electromyography.

Mexiletine likely improves electromyographic-based outcomes including degree of needle electromyographic myotonia detected. There was an improvement in the mexiletine group compared to the placebo group for both abductor digiti minimi and tibialis anterior (needle electromyographic abductor digiti minimi: MD −0.57, 95% CI −0.81 to −0.32; needle electromyographic tibialis anterior: MD −0.46, 95% CI −0.68 to −0.25; both 1 study, 59 participants; both moderate-certainty evidence; Analysis 2.3). We downgraded the certainty of the evidence for issues with applicability due to lack of clinical validation of needle electromyography. There was an improvement in the mexiletine group compared to the placebo group for myotonic discharges on needle electromyography using an average of a system of 0 to 3 grading, with 0 indicating no myotonic discharges and 3 indicating myotonic discharges with every insertion (MD −0.67, 95% CI −0.23 to −1.11; 1 study, 30 participants; moderate-certainty evidence; Analysis 2.3).

Adverse events

Four studies reported 94 adverse events in the mexiletine group and 29 adverse events in the placebo group (Kwiecinski 1992 (adverse events reported together for myotonic dystrophy type 1 and non-dystrophic myotonia); Statland 2012; Stunnenberg 2018; Vicart 2021; see Table 3; low-certainty evidence). We downgraded the certainty of the evidence due to risk of bias and imprecision. The most frequent adverse events with mexiletine were gastrointestinal symptoms and headaches; while there were some rare electrocardiogram changes and palpitations reported, there were no serious cardiac events. Vicart 2021 did not report specific adverse events for the placebo group.

Quality of life

Two studies reported quality of life as SF-36 (PCS and MCS) and the INQoL score (Statland 2012; Stunnenberg 2018). We pooled the results of the two trials using random-effects meta-analysis

for SF-36 PCS and INQoL score. For the SF-36 MCS score, due to an indication of potential carry-over effects, we presented results separately by treatment period for Statland 2012. Stunnenberg 2018 had no significant randomisation order or period effect so we presented results from both treatment periods. Therefore, we did not pool the results of the two trials in a meta-analysis; results by treatment period and overall are presented in forest plots in Analysis 2.4.

There may be an improvement in the mexiletine group compared to the placebo group in SF-36 PCS (MD 6.45, 95% CI 4.32 to 8.58; 2 studies, 89 participants; low-certainty evidence; Analysis 2.4). There was no difference between the mexiletine and placebo groups in INQoL score, but the 95% CIs were wide, including advantages to both mexiletine and placebo (MD −7.35, 95% CI −18.44 to 3.74; 2 studies, 89 participants; low-certainty evidence; Analysis 2.5). There was no difference between the mexiletine and placebo groups in SF-36 MCS in the first treatment period (MD −0.35, 95% CI −5.75 to 5.05; 1 study, 59 participants; low-certainty evidence; Analysis 2.4), but there was an improvement in the mexiletine group compared to the placebo group in the second treatment period and the entire treatment period (second treatment period: MD 10.40, 95% CI 0.80 to 20.00; 1 study, 59 participants; entire treatment period: MD 6.78, 95% CI 1.89 to 11.67; 1 study, 30 participants; both low-certainty evidence; Analysis 2.4). We downgraded the certainty of the evidence for inconsistency and imprecision.

Statland 2012 also reported other domain scores of the SF-36 and INQoL. Particular domains where there was an improvement with mexiletine compared to placebo were Physical Function, Physical Role, and Social Function (SF-36) and muscle locking, pain, fatigue, activity, independence, social relations, emotions, body image, perceived treatment effect, and expected treatment effect (INQoL).

Vicart 2021 reported within-group differences rather than between-group differences, limiting incorporation into our meta-analysis. The INQoL overall quality of life (aggregation of the five life subdomains) was improved after mexiletine treatment (from 47.8 to 27.1; P < 0.001).

Lamotrigine versus placebo in non-dystrophic myotonias

Andersen 2017 recruited 26 people with non-dystrophic myotonia into a cross-over trial comparing lamotrigine 300 mg daily versus placebo. They calculated an initial sample size of 42 participants; however, after interim analysis with defined stopping criteria, the study was stopped at 26 participants. It was not described whether the initial sample size calculation accounted for an interim analysis in calculating the sample size and hence the half-way number. The inclusion criteria, exclusion criteria, randomisation, and blinding procedures were well described. Block randomisation was undertaken. Four participants were lost to follow-up. Two participants used escape medications during the placebo period except on evaluation days.

See Summary of findings 3.

Primary outcome

Improvement in participant-reported clinical myotonia

We are very uncertain about the effect as comparative data were not reported using a validated scale.

The Myotonia Behaviour Score is a validated participant-reported scale in this cohort and is consistent with our primary outcome. The mean Myotonia Behaviour Score decreased by 29% after treatment with lamotrigine with a number needed to treat for an additional beneficial outcome of 3 (P = 0.006, 26 participants; standardised mean difference of the change from baseline in Myotonia Behaviour Score 1.5, 95% CI 1.2 to 1.8). However, the data did not appear to be adjusted for cross-over effect, and only within-group results (i.e. the change from baseline following treatment with lamotrigine) were available. There were no results of lamotrigine compared to placebo reported (Andersen 2017).

Secondary outcomes

Relaxation time

One study measured relaxation time as hand grip and eyelid closure (seconds) and reported them as log-transformed effect sizes (Andersen 2017). There may be an improvement in relaxation time with lamotrigine compared to placebo (hand grip: MD −2.80 (log) seconds, 95% CI −3.51 to −2.09; eyelid closure: MD −2.30 (log) seconds, 95% CI −2.81 to −1.79; 1 study, 22 participants; low-certainty evidence; Analysis 3.1). We downgraded the certainty of the evidence due to imprecision and issues with applicability.

Electromyographic relaxation time

No studies reported electromyographic relaxation time.

Adverse events

One study reported adverse events (Andersen 2017). There were 44 adverse events amongst 13 participants in the lamotrigine group and 23 adverse events amongst eight participants in the placebo group (Table 3; moderate-certainty evidence). We downgraded the certainty of the evidence due to imprecision. One participant had an allergic reaction (rash, myalgia), which reversed after medication cessation. The most common advert events with lamotrigine were headache, fatigue, and rash.

Quality of life

One study reported quality of life using the SF-36 (Andersen 2017). Quality of life is likely to improve after treatment with lamotrigine compared with placebo (MD 5.00, 95% CI 3.12 to 6.88; 1 study, 22 participants; moderate-certainty evidence; Analysis 3.2). Particular domains that were responsive included physical functioning and social function. We downgraded the certainty of the evidence due to imprecision.

Other interventions compared to placebo in myotonic dystrophy type 1

Clomipramine versus placebo in myotonic dystrophy type 1

One cross-over trial compared clomipramine to placebo in 17 people with myotonic dystrophy type 1 (Antonini 1990). The study excluded people with cardiac, ophthalmological, or urological diseases. Given that these systems can be involved in myotonic dystrophy, the study cohort was select and may have limited generalisability. The method of randomisation, allocation concealment, and the specifics of how randomisation was undertaken were not described. This trial had two washout intervals of 30 days, so the risk of a carry-over effect was reduced. The authors stated that there were no differences between people receiving clomipramine in the first or second treatment period; however, baseline characteristics were not provided for review. The

data of 15/17 participants were analysed and presented. Therefore, the certainty of the evidence for clomipramine versus placebo was low due to risk of bias and issues with generalisability.

Primary outcome

Improvement in participant-reported clinical myotonia

The study did not report improvement in clinical myotonia using a validated participant-reported scale.

Secondary outcomes

Relaxation time

The study used hand grip to measure relaxation time. Eight participants showed improvement on both clomipramine and placebo, one participant showed no improvement on both clomipramine and placebo, five participants showed improvement on clomipramine but not on placebo, and one participant showed improvement on placebo but not on clomipramine. There was no difference between treatment groups, but this result was very imprecise and important differences between treatments could not be ruled out (Mantel-Haenszel odds ratio (accounting for the cross-over design) 5.00, 95% CI 0.58 to 42.80; P = 0.14) (Antonini 1990). The analysis of a secondary outcome with a paired t-test (cross-over study) demonstrated that the mean relaxation time after clomipramine was shorter (P = 0.02) than after placebo (MD −6.69, 95% CI −12.82 to −0.56; low-certainty evidence; Analysis 4.1).

Electromyographic relaxation time

The study did not report electromyographic relaxation time.

Adverse events

The study reported the minor adverse events of drowsiness (6/15 (40%) participants with clomipramine versus 0/15 (0%) with placebo), dry mouth (2/15 (13%) with clomipramine versus 0/15 (0%) with placebo), tiredness (2/15 (13%) with clomipramine versus 2/15 (13%) with placebo), hyperhidrosis (1/15 (7%) with clomipramine versus 0/15 (0%) with placebo), and dizziness (1/15 (7%) with clomipramine versus 0/15 (0%) with placebo; Table 2; low-certainty evidence).

Quality of life

The study did not report quality of life.

Metformin versus placebo in myotonic dystrophy type 1

One study compared metformin to placebo in 40 people with myotonic dystrophy type 1 (Bassez 2018). This was a single-centre, randomised place-controlled trial. Inclusion and exclusion criteria were clearly defined and included ambulatory people with genetically confirmed myotonic dystrophy type 1. Randomisation procedures were well described with stratified randomisation (age, gender, distance walked) with appropriate blinding and allocation concealment. While the primary outcome was mobility based on the Six-Minute Walk Test, myotonia was a secondary outcome. Two participants withdrew early from the study and were not included in the analysis; a per-protocol analysis was also undertaken for myotonia.

Primary outcome

Improvement in participant-reported clinical myotonia

The study did not report improvement in clinical myotonia using a validated participant-reported scale.

Secondary outcomes

Relaxation time

The study reported relaxation time after hand grip contraction at 70% of maximal voluntary contracture sustained for five seconds, measured by dynamometer and reported as medians and interquartile ranges. In the intention-to-treat population, the placebo group had a median reduction of 2.20 ms in relaxation time compared to 21.20 ms in the metformin group (P = 0.787), and interquartile ranges around the median change from baseline in relaxation time on both placebo and metformin were wide. Therefore, the certainty of the evidence was moderate due to imprecision.

Electromyographic relaxation time

The study did not report electromyographic relaxation time.

Adverse events

The most frequent serious adverse events were diarrhoea (15 with metformin versus 5 with placebo), abdominal pain (10 with metformin versus 6 with placebo), and dyspepsia (4 with metformin versus 0 with placebo) (Table 2; moderate-certainty evidence).

Quality of life

There was an advantage in favour of metformin over placebo in the overall INQoL quality of life measure as well as perceived and expected treatment effects in the intention-to-treat population. Data were reported as medians and interquartile ranges, and the interquartile ranges around the median change from baseline in quality of life on both placebo and metformin were wide. Therefore, the certainty of the evidence is moderate due to imprecision.

Imipramine versus placebo in myotonic dystrophy type 1

One cross-over trial recruiting 12 participants with myotonic dystrophy type 1 compared imipramine to placebo (Gascon 1989). The trial measured both left- and right-hand relaxation times after imipramine and placebo. The trial inclusion and exclusion criteria were not clearly stated. The study did not describe the method of randomisation to the intervention or method of blinding. One participant dropped out due to having a normal relaxation time. This trial did not have a washout period; therefore, there is a strong possibility of a carry-over effect. Overall, the trial was at high risk of bias. Furthermore, the first arm treatment data (prior to cross-over) were not available, so only descriptive results could be presented. Therefore, the certainty of the evidence for imipramine versus placebo in myotonic dystrophy type 1 was low due to serious risk of bias including a likely carry-over effect.

Primary outcome

Improvement in participant-reported clinical myotonia

The study did not report improvement in clinical myotonia using a validated participant-reported scale.

Secondary outcomes

Relaxation time

The primary outcome of this trial was relaxation time after hand grip after squeezing two fingers for two to three seconds. For the right hand, five participants showed improvement on both imipramine and placebo, six participants showed improvement on imipramine but not on placebo. For the left hand, six participants showed improvement on both imipramine and placebo, one participant showed no improvement on both imipramine and placebo, and four participants showed improvement on imipramine but not on placebo. None of the participants showed improvement on placebo and not on imipramine (Gascon 1989). The MD in relaxation time in the right hand between imipramine and placebo was 1.07, and in the left hand was 0.73 favouring imipramine. This was reported as "statistically significant" using the Newman-Keuls multiple range test. Time to relax after eliciting percussion myotonia was also recorded. Both outcomes, based on instructions to participants and visualisation by the examiner, were subject to substantial inter-user error and were difficult to standardise.

Electromyographic relaxation time

The study did not report electromyographic relaxation time.

Adverse events

The 'most important' adverse events reported were dry mouth (8/12 (67%) participants with imipramine versus 2/12 (17%) with placebo), dizziness (4/12 (33%) with imipramine versus 1/12 (8%) with placebo), increased sweating (4/12 (33%) with imipramine versus 3/12 (25%) with placebo), constipation (4/12 (33%) with imipramine versus 1/12 (8%) with placebo), tremor (3/12 (25%) with imipramine versus 1/12 (8%) with placebo), blurred vision (3/12 (25%) with imipramine versus 0/12 (0%) with placebo), and diarrhoea (3/12 (25%) with imipramine versus 2/12 (17%) with placebo) (Gascon 1989; Table 2; low-certainty evidence).

Quality of life

The study did not report quality of life.

Nifedipine versus placebo in myotonic dystrophy type 1

One cross-over trial recruiting 10 participants with myotonic dystrophy type 1 compared nifedipine 10 mg three times daily, nifedipine 20 mg three times daily, and placebo (Grant 1987). This was a single-blind study. Randomisation, method of allocation concealment, and blinding were not described. This trial did not have a washout period; therefore, there is a strong possibility of a carry-over effect. First-period treatment data (prior to cross-over) were not available for this trial, so we presented a narrative summary of results only. Due to the risks described and the sample size, this study was at high risk of bias. The certainty of the evidence for nifedipine versus placebo in people with myotonic dystrophy type 1 was low due to serious risk of bias including a likely carry-over effect.

Primary outcome

Improvement in participant-reported clinical myotonia

The study did not report improvement in clinical myotonia using a validated participant-reported scale.

There was improvement in myotonia on finger extension time with nifedipine compared to placebo that did not reach statistical significance. Five participants reported improvement in myotonia with nifedipine 10 mg and five participants reported improvement in myotonia with nifedipine 20 mg. No participants reported worsening of myotonia with nifedipine (10 mg or 20 mg). One participant reported an improvement, seven participants reported no change, and two participants reported worsening myotonia with placebo.

Secondary outcomes

Relaxation time

The study did not report relaxation time.

Electromyographic relaxation time

The study did not report electromyographic relaxation time.

Adverse events

Minor adverse events reported were headache and lethargy with nifedipine 20 mg (20% (2/10)) and light T-wave flattening or T-wave inversion on the electrocardiogram on both doses of nifedipine (10% (1/10)) (Table 2; low-certainty evidence).

Quality of life

The study did not report quality of life.

Taurine versus placebo in myotonic dystrophy type 1

One cross-over trial recruiting nine participants with myotonic dystrophy type 1 compared taurine to placebo (Durelli 1983). The trial was double-blind; however, the method of randomisation was not described. This trial did not have a washout period; therefore, there is a strong possibility of a carry-over effect. First-period treatment data (prior to cross-over) were not available for this trial, so we presented a narrative summary only. The certainty of the evidence for taurine versus placebo in myotonic dystrophy type 1 was low due to serious risk of bias including a likely carry-over effect.

Primary outcome

Improvement in participant-reported clinical myotonia

The study did not report improvement in clinical myotonia using a validated participant-reported scale.

Secondary outcomes

Relaxation time

The study did not report relaxation time.

Electromyographic relaxation time

The study measured electromyographic relaxation time and treatment with taurine showed a lower time than both the baseline and placebo (low-certainty evidence).

Adverse events

There were no adverse events reported with taurine or placebo (Table 2; low-certainty evidence).

Quality of life

The study did not report quality of life.

Other interventions compared to placebo or control (descriptive results)

The remaining studies did not present any data that could be used in the review (due to lack of washout period or incomplete results). We briefly summarised the interventions, conclusions, and adverse events reported in these studies below. The certainty of the evidence for these other interventions compared to placebo or control was very low due to the limited information available and serious risk of bias in all the studies.

Summary of trials and main conclusions

One cross-over trial recruiting 10 participants compared procainamide and disopyramide (Finlay 1982). The trial authors concluded that disopyramide was at least as effective as procainamide in the relief of myotonia (hand opening and grip strength) and that two participants who could not tolerate procainamide both tolerated disopyramide.

One cross-over trial recruiting 20 participants compared quinine, procainamide, prednisone, and placebo (Leyburn 1959). The trial authors concluded that all three drugs had a therapeutic effect in reducing the duration of the myotonic after-contraction. Quinine was judged the least effective, and procainamide and prednisone were equally effective, but prednisone was more likely to cause adverse effects when used over a long time. Most participants experienced improvement in myotonia with all three treatments (ranging between 10% and 100% improvement). The study did not present data for the placebo group.

One cross-over trial recruiting 20 participants compared diazepam and placebo (Lewis 1966). The trial showed a large placebo effect and research into the placebo tablets identified that they contained quinine sulphate 0.5 mg per tablet. This substance could be an effective treatment for myotonia, resulting in performance bias. The trial authors concluded that diazepam may be useful in selected patients with disorders of muscle relaxation, but it cannot be recommended as a standard therapeutic agent in treatment of myotonia at this time.

One cross-over trial recruiting 30 participants compared mexiletine, phenytoin, disopyramide, tocainide, and placebo (Kwiecinski 1992). The trial authors concluded that mexiletine and tocainide appeared to be the most 'potent' antimyotonic agents in terms of subjective and objective measures of response, but due to the risks of haematological problems, tocainide should not be used for the treatment of myotonia.

One cross-over trial recruiting nine participants compared diphenylhydantoin, procainamide, and placebo (Munsat 1967). The trial authors concluded that diphenylhydantoin was as effective as procainamide in relieving myotonia, both subjectively and objectively, and that diphenylhydantoin was better tolerated than procainamide.

Summary of adverse events reported on interventions

The reported adverse events in the trials for which other outcome data were not available were as follows (summarised in alphabetical order of the drugs).

- Diazepam: 64% (7/11 participants) had sedation and 27% (3/11) had dizziness (Lewis 1966).
- Diphenylhydantoin: none stated (Munsat 1967).
- Disopyramide: 32% (7/22) had dry mouth and blurred vision while taking high doses (Finlay 1982; Kwiecinski 1992).
- Phenytoin: 10% (3/30) had skin rash, somnolence, and mild ataxia (Kwiecinski 1992).
- Prednisone: no adverse events reported in three weeks; trial authors emphasise that hazards with long-term therapy with this drug were possible (Leyburn 1959).
- Procainamide: 39% (15/39) had gastrointestinal complaints (Finlay 1982; Leyburn 1959; Munsat 1967; Shields 1988).
- Quinine: 45% (9/20) had mild and tolerable tinnitus, 30% (6/20) had some degree of deafness, and 5% (1/20) had a dull head without tinnitus (Leyburn 1959).
- Tocainide: 6% (1/18) had lymphadenopathy, and 11% (2/8) had dizziness, anxiety, and tremor (Kwiecinski 1992; Soff 1987).

DISCUSSION

Summary of main results

See Summary of findings 1; Summary of findings 2; Summary of findings 3.

With the first trial exploring treatment of myotonia published in 1959 (Leyburn 1959), the initial clinical trials in myotonia were small with significant bias and inadequate procedures relating to aspects such as randomisation and blinding. Various medications were trialled predominantly based on a theoretical basis for efficacy, such as mode of action on ion channels. Calcium channel blockers, such as nifedipine, and tricyclic antidepressants, such as clomipramine and imipramine, did show treatment benefit for myotonia but were limited in trial design, with significant bias (Antonini 1990; Gascon 1989; Grant 1987). One small trial with taurine was effective but included only nine participants with study design, reporting, and bias limitations (Durelli 1983). Acetazolamide also demonstrated efficacy, but in a small trial (Markhorst 2014).

The first well-conducted trial was in 2010 when Logigian and colleagues reported improved relaxation times after hand grip in people with myotonic dystrophy type 1 treated with mexiletine (Logigian 2010a; Logigian 2010b). While relaxation time had not been validated in this cohort, Logigian and colleagues used a computerised algorithm to record the relaxation time that was more reproducible than observer-recorded relaxation time. However, a more-recent, well-conducted study by Heatwole and colleagues found no significant improvement in myotonia with mexiletine in myotonic dystrophy type 1 (Heatwole 2021). Both studies showed good safety and tolerability in people receiving mexiletine.

Statland and colleagues was a pivotal study in non-dystrophic myotonias, which was the earliest well-conducted study to show the efficacy of mexiletine in this cohort of patients (Statland 2012). Further studies have supported this finding of efficacy of mexiletine in non-dystrophic myotonias (Stunnenberg 2018). Overall, mexiletine is effective and well tolerated for treatment of myotonia in people with non-dystrophic myotonia. One study has shown efficacy of lamotrigine in this group (Andersen 2017). However, the study size was small as it was stopped early due to efficacy. Reproduction of these results is needed to further support this finding.

Seven of the trials were newly identified and included for this update (Andersen 2017; Bassez 2018; Heatwole 2021; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018; Vicart 2021). Four of these trials looked exclusively at people with non-dystrophic myotonia, investigating the effect of mexiletine or lamotrigine (Andersen 2017; Statland 2012; Stunnenberg 2018; Vicart 2021). Further randomised studies explored mexiletine in myotonic dystrophy (Heatwole 2021; Logigian 2010a; Logigian 2010b). On the basis of these studies, mexiletine appears to be safe and is likely an effective treatment for symptomatic management of myotonia in non-dystrophic myotonia and myotonic dystrophy. Lamotrigine also appears to be effective in non-dystrophic myotonia. In general, both drugs were well tolerated; however, the quality of reporting of adverse events was inadequate. Where reported, the most common adverse effects of mexiletine were epigastric symptoms and headache. The adverse effects associated with lamotrigine included headache, skin rash/itch, and fatigue, but the number of days with adverse effects was similar between the treatment and placebo groups. The certainty of the evidence for all findings was moderate to low.

Overall completeness and applicability of evidence

The more-recent studies of mexiletine and lamotrigine were better powered, with more robust analyses. Head-to-head trials comparing mexiletine and lamotrigine in non-dystrophic myotonia are ongoing. The older studies were generally small with a high risk of bias. Studies of other medications, including phenytoin, imipramine, procainamide, clomipramine, nifedipine, tocainide, diazepam, quinine, diphenylhydantoin, and taurine, were inadequately powered with significant bias and did not show efficacy in the treatment of myotonia.

This review consists overall of more participants with myotonic dystrophy type 1 compared to non-dystrophic myotonias (219 versus 173). This likely reflects the higher prevalence of myotonic dystrophy type 1 compared to non-dystrophic myotonia. However, the impact on quality of life from myotonia is more significant and troublesome to people with non-dystrophic myotonias (Trivedi 2013). While earlier studies combined both myotonic dystrophy type 1 and non-dystrophic myotonia, more robust studies had only one condition in the inclusion criteria.

Non-dystrophic myotonias in particular are a rare group of genetic conditions with a limited pool of affected people. Recruitment to meet sample size is a challenge. A particular challenge in more-recent trials is the need to stop pre-existing treatments to commence clinical trials. There is often patient reluctance to cease mexiletine or undertake washout periods.

Additionally, most trials excluded people who had systemic conditions, including cardiac conditions, which limits the applicability and generalisability of results to people without these comorbidities. The exclusion criteria for one trial stated that people with myotonic dystrophy type 1 with a history of cardiac or ophthalmological disease were excluded (Antonini 1990). As cardiac and ophthalmological diseases occur frequently in people with myotonic dystrophy type 1, it is possible that the population in the trial is not representative of the general myotonic dystrophy type 1 population. Furthermore, genetic diagnosis is often not available to all patients. This is reflected in Heatwole 2021, where the inclusion criteria were modified during the trial to include people who did not have a genetic diagnosis in order to allow more patients to be eligible and be recruited. This may create some heterogeneity in trials, and it may be useful at a minimum to retrospectively confirm a genetic diagnosis in patients.

One of the major challenges in trials in general is using a responsive and relevant primary outcome measure that has been validated in the cohort. Both the Interactive Voice Response Diary and Myotonia Behaviour Score have been validated in people with non-dystrophic myotonia. The grip relaxation time is difficult to standardise, particularly if recorded by an observer. A computer algorithm to record relaxation time may allow this outcome measure to be more reliable, but requires validating in natural history studies. Moreover, warm-up phenomena and paradoxical warm-up can skew measures of myotonia. Warm-up phenomena occur in myotonia congenita where myotonia improves with repeated contraction, and paradoxical myotonia occurs in paramyotonia congenita where myotonia worsens with repeated use. Standardising for these phenomena is a challenge and stratification in randomising these subgroups as well as subgroup analyses should also be considered.

Quality of the evidence

The overall certainty of the evidence in the earlier trials was very low and not adequate to allow firm conclusions to be drawn. Common sources of bias were use of unvalidated outcome measures, inadequate description of blinding and randomisation, and lack of adjustment for cross-over or period effect. The methods and inclusion and exclusion criteria were typically not reported in sufficient detail. Some studies had small numbers and with descriptive results only (Finlay 1982) or in abstract form (Kratz 1986), so it was not possible to draw conclusions. One of the studies had a large placebo effect, which made further analysis difficult (Lewis 1966). Many of the earlier cross-over studies did not include washout intervals, which meant that there was a strong possibility of a carry-over effect (Durelli 1983; Gascon 1989; Grant 1987; Kwiecinski 1992; Leyburn 1959; Munsat 1967). Data from the first treatment arms (prior to cross-over) were not presented for any of these studies; data were inappropriately presented in the form of combined results of both active treatment arms and both placebo arms. Some studies had mixed populations and typically the subgroups were not defined adequately.

The most common trial design used was a cross-over design, which is appropriate in assessing myotonia in non-dystrophic myotonias. A cross-over design allows people with non-dystrophic myotonia to be internal controls, which is important in a condition with significant heterogeneity of symptoms. However, allowing for washout and adjusting or assessing for period effect is key. A parallel group design was more likely to be used for trials in people with myotonic dystrophy type 1, which is appropriate given the potential for progression of the underlying disease and some studies also assessed mobility.

Overall, the more-recent studies with larger participant numbers used clinically validated primary outcome measures with a robust design and moderate certainty of evidence for mexiletine and lamotrigine in people with non-dystrophic myotonia (Andersen 2017; Heatwole 2021; Logigian 2010a; Logigian 2010b; Statland 2012; Stunnenberg 2018). However, several smaller studies using other treatment modalities had several sources of bias, design concerns, inconsistencies, or did not use validated outcome scores, which reduced the quality and certainty of the data. There

was moderate-certainty evidence for symptomatic treatment with mexiletine for myotonia in non-dystrophic myotonias, downgraded using the GRADE approach particularly for selective reporting of outcomes. One study did not describe blinding well. There was low- to moderate-certainty evidence for mexiletine for the treatment of myotonia in myotonic dystrophy with selective or incomplete reporting of outcomes. There was low-certainty evidence showing lamotrigine to be effective for symptomatic treatment of non-dystrophic myotonias due to small sample size and unclear sample size power taking into account the interim analysis.

Potential biases in the review process

The review process was undertaken using rigorous processes outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* with several investigators from independent institutions to reduce bias (Higgins 2022).

Agreements and disagreements with other studies or reviews

Expert opinion at present is consistent with these findings, with mexiletine being the gold standard for the symptomatic treatment of myotonia (Desaphy 2021). Retrospective reviews have also supported the finding of safety of mexiletine use (Suetterlin 2015). While there is increasing use of lamotrigine for the management of myotonia due to ease of access, familiarity, and tolerability, the efficacy compared to mexiletine remains unknown. The heterogeneity of the included groups across studies suggests a need for better stratification in trials leading potentially to more personalised treatments based on genotype or predominant symptoms (Desaphy 2021).

Since the search date and initial submission of this review, MEND: MExiletine versus lamotrigine in Non-Dystrophic myotonia has been published (Vivekanandam 2024). The study findings are in line with the conclusions of this review by supporting the utility of mexiletine and lamotrigine for symptomatic treatment of myotonia. Subsequent updates of this review will incorporate this and further completed studies.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence for symptomatic treatment with mexiletine for myotonia in non-dystrophic myotonias. There is some low- to moderate-certainty evidence for mexiletine in the treatment of myotonia in myotonic dystrophy type 1. However, more-recent studies did not reproduce these findings. Overall, mexiletine seems to be well tolerated in both myotonic conditions. Low-certainty evidence has shown lamotrigine to be effective for symptomatic treatment of non-dystrophic myotonias in one study. Lamotrigine is well tolerated in non-dystrophic myotonias. There is very limited, uncertain evidence to support the use of other agents without further larger, well-conducted studies. Overall, mexiletine and lamotrigine are treatment options for myotonia in non-dystrophic myotonias. Head-to-head trials comparing lamotrigine and mexiletine in non-dystrophic myotonias are ongoing and are likely to determine first-line treatment or provide a comparative evidence base for clinical practice.

Implications for research

With two effective medications with well-conducted studies, there is clinical equipoise in regard to the most effective treatment option. Additionally, the data suggest that not all patients respond to therapy and research into aetiology and treatment options for non-responders is needed. Moreover, the studies, in particular the small numbers of most trials, highlight the challenges in recruitment and design of robust trials in rare diseases, and research into trial design to improve recruitment in rare diseases will be important for future trials.

Trials comparing mexiletine and lamotrigine in people with non-dystrophic myotonias are currently ongoing (NCT05017155; NCT05639257). This will be helpful in producing reproducible results for lamotrigine in non-dystrophic myotonias and determining which sodium channel blocker is preferred for treating myotonia. In the future, as patients are already on treatment with mexiletine or lamotrigine, it will become increasingly difficult to conduct trials on treatment-naive people or find people who are willing to stop treatment. Additionally, given that there are now treatment options for myotonia, the real area of need in the future will be for people who are non-responders to mexiletine. Other agents that have not been tested in randomised controlled trials, such as acetazolamide, flecainide, ranolazine, and lacosamide, will be needed when planning future clinical trials. Current trials looking at the efficacy of mexiletine in children with non-dystrophic myotonia are also underway. While mexiletine is currently used with anecdotal evidence of efficacy in paediatric medicine, there are no well-conducted trials demonstrating efficacy.

Tideglusib inhibits glycogen synthase kinase (GSK3β), which is dysregulated in multiple tissues in myotonic dystrophy type 1. It has been shown to be safe in small groups of people and further trials are ongoing and planned (NCT03692312).

As genetic treatments become increasingly used in neuromuscular disorders, the myotonic conditions that are single gene disorders are attractive candidates for therapy. While this is still in the early stages, we have seen a rapid increase in potential therapies since the late 2010s.

With so many potential treatments and limited pools of patients, innovative trial designs that are well conducted will be key to delineating optimal treatments for myotonia. Additionally, stratification of patients based on genotype to ensure therapy is suited to their affected channel, combined with innovative trial algorithms, is likely to be useful in studies of rare diseases.

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andersen 2017

Study characteristics	
Methods	Double-blind, randomised, cross-over trial
Participants	Setting: adults with myotonia congenita or paramyotonia congenita registered at Copenhagen University Hospital invited by letter and all who responded positively were asked to invite family members. Inclusion criteria: adults aged > 18 years, genetically confirmed myotonia congenita or paramyotonia congenita, and obvious myotonia in eye, hand, or leg muscles, which affected daily living Exclusion criteria: contraindications to treatment with lamotrigine, e.g. known allergy, reduced kidney or liver function, other concomitant treatments, or conditions that could potentially interact with lamotrigine (epilepsy, long QT-interval on ECG), participation in other treatment studies < 30 days before enrolment, pregnancy or breastfeeding Age: > 18 years; range 19–74 years Sex: group 1 (lamotrigine): males 6, females 7; group 2 (placebo): males 10, females 3 26 participants
Interventions	Lamotrigine (increasing doses from 25 mg, 50 mg, 150 mg, to 300 mg)

Andersen 2017 *(Continued)*

	Placebo Randomised controlled trial: randomised to 2 × 8-week periods of treatment with first lamotrigine then placebo (group 1) or vice versa (group 2)
Outcomes	**Primary outcome** *Myotonia Behaviour Scale* **Secondary outcomes** *Clinical myotonia of eye closure* The eyelid muscle relaxation time was measured after 5 seconds of maximal contraction. After the command 'open' participants should open their eyelids as fast as possible. The time from closure to fully open eyes was determined 5 times. *Clinical myotonia of hand closure* The relaxation time of hand muscles was performed the same way. After 5 seconds of tight closure of the dominant hand, the time from the command 'open' to fully stretching of all 5 fingers was determined 5 times. The 5 repetitions were performed to identify the warm-up phenomenon. The treatment effect was calculated from the highest relaxation time, if the warm-up phenomenon occurred, or otherwise as the average of the 5 relaxation times. *Timed Up and Go test* First, the modified Timed Up and Go test was performed after 10 minutes of rest in the chair, measuring the time it took participants to stand up, walk 3 m, and then return to sitting in the chair at their usual pace. *14-step stair test* Participants walked 14 steps up the stairs and returned to the base as fast as possible. Normal values of the 4 timed tests were obtained in a linear-mixed cohort of non-myotonic participants (age: 20–70, 11 males, 10 females). *SF-36* *Serum creatin kinase* *Use of escape medication* Escape medication was noted in the diary during the trial.
Funding	The Jascha Foundation, Aase and Einar Danielsens Foundation, Augustinus Foundation, and A. P. Moeller Foundation
Conflicts of interest among principal investigators	Quote: "G.A. declares no competing interest. G.H. declares no competing interest. N.W. received research support from the Danish Council for Independent Research in Medical Sciences. M.D. declares no competing interest. H.A. has received research, travel support and speaker honoraria from Octapharma, CSL Behring, Pfizer and Genzyme/ Sanofi, and has served as consultant on advisory board of UCB Pharma within the last 3 years. J.V. has received research and travel support and speaker honoraria from Genzyme/Sanofi and Ultragenyx Pharmaceuticals, and has acted as consultant on advisory boards for Genzyme/ Sanofi, Sarepta, Lundbeck, Ultragenyx Pharmaceuticals, NOVO Nordisk, aTyr Pharma and Alexion Pharmaceuticals within the last 3 years."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Andersen 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Clearly described – independent pharmacy.
Allocation concealment (selection bias)	Low risk	Clearly described, an independent pharmacy (Glostrup Apotek), without any contact to the trial participants, generated the random allocation sequence.
Blinding of participants and personnel (performance bias)	Low risk	Blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinded; however, due to the nature of the treatments, there is a risk of unintentional self-unblinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Described clearly.
Selective reporting (reporting bias)	Low risk	No bias.
Other bias	Unclear risk	Unclear if interim analysis was taken into sample size calculation.

Antonini 1990

Study characteristics	
Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in Italy Treatment period: 33 days. Total duration: 166 days Results presented as combined data from both active treatment arms and both placebo arms. 2 washout periods of 30 days. Results of first arms reported
Participants	17 participants with 2 withdrawals 17 people with myotonic dystrophy 8 males, 9 females Mean age: 29 (SD not stated) Inclusion criteria: well-established criteria for myotonic dystrophy Exclusion criteria: with cardiac, ophthalmological, or urological diseases
Interventions	Clomipramine 75 mg/day Placebo
Outcomes	Grip myotonia by relaxation time in seconds. Time necessary to completely open the fist after 3 seconds of maximum voluntary contraction performed by maintaining a constant pressure in a rolled sphygmomanometer cuff.
Funding	Not mentioned in text

Antonini 1990 *(Continued)*

Conflicts of interest among principal investigators	Not mentioned in text
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear, not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all included participants were analysed. Quote: "One subject receiving clomipramine and 1 receiving placebo did not complete the study because of poor compliance."
Selective reporting (reporting bias)	Low risk	No selective reporting, result first arm cross-over study stated.
Other bias	Low risk	2 washout periods of 30 days.

Bassez 2018

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial
Participants	40 people with myotonia dystrophy 1 (38 received ≥ 1 dose of medication), 29 completed 1 year follow-up, 15/38 were excluded from intention to treat Age: 18–60 years Sex: placebo group: females 11/19 (57.89%); metformin group: females 11/19 (57.89%) Inclusion criteria: diagnosis of DM1, confirmed by DM1 genetic mutation Adults aged ≥ 18 to ≤ 60 years Muscular Impairment Rating Scale score 2 or 3 Ambulatory, able to perform the 6-Minute Walk Test All laboratory parameters must have been grade 0 or 1 (as per Common Terminology Criteria for Adverse Events criteria) except for aspartate aminotransferase, alanine aminotransferase for which a grade 2 would have been allowed if stated non-clinically significant

Bassez 2018 *(Continued)*

	For women of child-bearing potential, i.e. with no history of hysterectomy or tubal ligation, use of 1 effective method of contraception during the conduct of the study Exclusion criteria: serious concomitant medical disorder; evidence of renal dysfunction (creatinine clearance < 60 mL/minute); blood dyscrasia; hepatic insufficiency; symptomatic pancreatitis; cardiac diseases not controlled; congestive heart failure (New York Heart Association score > 3); cardiac rhythm anomalies (supraventricular or ventricular) not controlled or severe conduction abnormalities (atrioventricular block I, II or III or His-ventricle > 70 ms) without medical device (people with pacemaker could be included) (echocardiography in the year before the inclusion); congenital heart defect; history of myocardial infarction, metabolic acidosis, hypertension, significant central nervous system impairment, or neurodegenerative or neuromuscular disease other than DM1; history of psychiatric conditions including, but not limited to, psychosis, suicidal ideations, or major depression (people with mild-to-moderate depression in the past may have been enroled if, in the Investigator's opinion, they were suitable for treatment); drug or alcohol abuse within 12 months of enrolment; other medical condition (besides DM1) that would significantly impact ambulation; history of malignancy except for cases of remission (remission > 12 months) and surgically cured skin cancer or pilomatricoma (benign tumour of the hair follicle that is associated with DM1); vital capacity < 60% or total lung capacity < 60%, hypercapnia (partial pressure of carbon dioxide ≥ 50 mmHg) or other signs of poor respiratory status which is expected to require the initiation of bilevel positive airway pressure within the study period (people with nocturnal non-invasive ventilation continuous positive airway pressure or bilevel positive airway pressure could be included); use of medications intended for the treatment of DM1 including glucocorticoids, anabolic steroids, testosterone, growth hormone, or insulin-like growth factor I within 1 year of entry; any medical contraindications to metformin; known allergy to metformin or its excipients; symptomatic insulin requiring diabetes or type 2 diabetes requiring oral antidiabetic agents; pregnant or breastfeeding; participation in another experimental therapeutic protocol within 6 months prior to baseline and during the study period (participation in natural history study is allowed); any other condition that, in the opinion of the investigator, may compromise the safety or compliance of the patient or would preclude the patient from successfully completing.
Interventions	Metformin Placebo
Outcomes	**Primary outcome** 6-Minute Walk Test **Secondary outcomes** Muscle function and strength Myotonia relaxation times Gait variables Social participation Quality of life
Funding	Centre d'Etude des Cellules Souches, a research entity funded by the AFM-Telethon charity
Conflicts of interest among principal investigators	The authors reported no competing interests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Bassez 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Described clearly – generated by clinical research organisation.
Allocation concealment (selection bias)	Low risk	Described clearly – randomisation sequence was generated by an independent clinical research organisation and, therefore, concealed from participants and personnel.
Blinding of participants and personnel (performance bias)	Low risk	Described clearly.
Blinding of outcome assessment (detection bias)	Low risk	Described clearly.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention to treat, lack of detail of drop-outs.
Selective reporting (reporting bias)	Low risk	No issues.
Other bias	Low risk	No other bias.

Durelli 1983

Study characteristics	
Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in Italy Treatment period: 6 months. Total duration: 1 year Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results of first arms not reported
Participants	9 participants without withdrawals 9 people with myotonic dystrophy Number of males and females not reported Mean age not reported Inclusion criteria: established clinical EMG criteria Exclusion criteria: none reported
Interventions	Taurine 100–150 mg/kg Placebo
Outcomes	EMG relaxation time after maximum voluntary contraction Occurrence of percussion myotonia Occurrence of myotonic discharges by electrical stimulation of median nerve

Durelli 1983 *(Continued)*

	Potassium chloride loading test in mmol per litre necessary for occurrence of myotonia
Funding	The work was partially supported by grants from Muscular Dystrophy Association of America. Inc, and from Istituto Farmochimico Falorni, SPA, Firenze, Italy.
Conflicts of interest among principal investigators	Not mentioned in text
Notes	No washout period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was assigned to either the placebo or the active-drug phase of the study." Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Taurine was given orally in doses of 100 to 150 mg per kilogram. Placebo capsules had the same appearance, odor, and taste as taurine capsules." Quote: "Both the patients and the physician who carried out the final examination were completely unaware of the results."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Taurine was given orally in doses of 100 to 150 mg per kilogram. Placebo capsules had the same appearance, odor, and taste as taurine capsules." Quote: "Both the patients and the physician who carried out the final examination were completely unaware of the results."
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	High risk	Result first arm cross-over study not stated.
Other bias	High risk	No washout period.

Finlay 1982

Study characteristics

Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in UK Treatment period: 14 days. Total duration: 28 days

Finlay 1982 *(Continued)*

	Results presented as descriptive, individual data for the 4 treatment arms. No washout period. Descriptive data first arms stated
Participants	10 participants with 2 withdrawals 10 people with myotonic dystrophy 7 males, 3 females Mean age not reported. Range 31–59 years Inclusion criteria: none reported Exclusion criteria: none reported
Interventions	Procainamide 250 mg 4 times daily first week and 500 mg 4 times daily second week versus disopyramide 100 mg 3 times daily first week and 200 mg 3 times daily second week Comparison between both treatments
Outcomes	Grip myotonia by measuring relaxation time in seconds necessary to completely open the fist after 3 minutes of maximum voluntary contraction Grip strength using an RAF Gripometer Subjective comments
Funding	Not stated in text
Conflicts of interest among principal investigators	Not stated in text
Notes	Individually continuous data not stated No statistical analysis Participants could recognise their original medicine by type of adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were divided at random into two groups; Group A received procainamide, Group B were given disopyramide. After 14 days treatment, patients were re-assessed, treatment reversed between the two groups and a re-assessment made after a further 14 days." Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	High risk	Quote: "Procainamide was supplied in 250 mg tablets and disopyramide base in 100 mg capsules. Patients were allowed to recognise differences between the medications. Thus where procainamide or disopyramide had been taken previously, the patients knew they were allocated to their usual medication. Otherwise, the patients were unaware of the nature of the medication prescribed. Treatment was coded and the code known only to the dispensing pharmacist."

Finlay 1982 *(Continued)*

Blinding of outcome assessment (detection bias)	High risk	Quote: "Procainamide was supplied in 250 mg tablets and disopyramide base in 100 mg capsules. Patients were allowed to recognise differences between the medications. Thus where procainamide or disopyramide had been taken previously, the patients knew they were allocated to their usual medication. Otherwise, the patients were unaware of the nature of the medication prescribed. Treatment was coded and the code known only to the dispensing pharmacist."
Incomplete outcome data (attrition bias) All outcomes	High risk	Results presented as descriptive. Completeness of data not described
Selective reporting (reporting bias)	High risk	Results presented as descriptive, individually continuous data not stated, no statistical analysis.
Other bias	High risk	No washout period.

Gascon 1989

Study characteristics	
Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in North Dakota, USA Treatment period: 6 weeks. Total duration: 12 weeks Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arm not stated
Participants	12/23 participants with myotonic dystrophy (confirmed by well-established criteria) 1 dropout because of normal relaxation time 6 males, 6 females Mean age not reported. Range 18–55 years Inclusion criteria: none reported Exclusion criteria: none reported
Interventions	Imipramine 50–375 mg/day on the basis of plasma concentrations Placebo
Outcomes	Grip myotonia by measuring relaxation time after squeezing the examiner's 2 fingers for 2–3 seconds Percussion myotonia thenar eminence after struck with reflex hammer by measuring time in seconds 3 successive timings of grip and percussion myotonia were taken, and the mean of these 3 was used as the participant's "score."
Funding	Grant from Neuropsychiatric Institute, Fargo, North Dakota

Gascon 1989 *(Continued)*

Conflicts of interest among principal investigators	Not mentioned in text
Notes	Small study without washout period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 12 patients were randomly assigned to one of two double-blind, crossover study conditions, placebo-imipramine or imipramine-placebo, each of which utilized a 6-wk treatment period."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear, not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 drop-out because of normal relaxation time.
Selective reporting (reporting bias)	High risk	Result first arm cross-over study not stated.
Other bias	High risk	No washout period.

Grant 1987

Study characteristics

Methods	Randomised, single-blind cross-over study Method of randomisation: not stated Single centre in Glasgow, Scotland Treatment period: 2 weeks. Total duration: unclear Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results for first arms not stated
Participants	10 participants with no withdrawals 10 people with myotonic dystrophy 6 males, 4 females Mean age: 40.4 years (SD not reported) Inclusion criteria: accepted clinical criteria and EMG characteristics

Grant 1987 *(Continued)*

	Exclusion criteria: none stated.
Interventions	Nifedipine 10 mg 3 times daily and nifedipine 20 mg 3 times daily Placebo.
Outcomes	Finger extension time of both hands measured as relaxation time after maximal voluntary contraction The mean value of the first 5 extension times was measured.
Funding	Not mentioned in text
Conflicts of interest among principal investigators	Not mentioned in text
Notes	Small study without washout period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Single blind. Not stated who was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Single blind. Not stated who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	High risk	Results of first arm not stated.
Other bias	High risk	No washout period.

Heatwole 2021

Study characteristics

Methods	Double-blind, randomised-controlled trial Setting: clinic Aged: 18–80 years 42 participants Sex: placebo group: 17/21 females; mexiletine group: 12/21 females

Heatwole 2021 *(Continued)*

	Inclusion criteria: age 18–80 years, had a genetically confirmed diagnosis of DM1, had isometric grip myotonia > 1 second, and were able to walk independently for 30 feet and walk continuously for > 6 minutes (walking stick, walker, orthoses allowed) at a distance over 100 m 2 eligibility criteria were modified during the study to allow more people with DM1 to be eligible for potential participation. Namely, participants were permitted to have a baseline 6-minute walk distance > 500 m and to have no genetic confirmation of DM1 if they had clinical symptoms of DM1 and a first-degree relative with positive genetic testing. Exclusion criteria: congenital onset of disease; treatment with mexiletine within the prior 8 weeks; second- or third-degree heart block; atrial flutter; atrial fibrillation; ventricular arrhythmias; ongoing medical treatment of a cardiac arrhythmia; concurrent antimyotonic drug use; liver or kidney disease; epilepsy; pregnancy; severe depression or suicidality; drug or alcohol abuse; severe arthritis; heart failure; cardiomyopathy; symptomatic coronary artery disease; 6-minute walk distance > 500 m; and cancer within the previous 5 years (other than benign skin cancer).
Participants	42 people with myotonia dystrophy 1
Interventions	Mexiletine 150 mg capsules orally, 3 times daily for 6 months Placebo capsules orally, 3 times daily for 6 months
Outcomes	**Primary outcome** 6-Minute Walk Test (change between baseline and 6 months) **Secondary outcomes** Hand grip relaxation time, recorded as the time interval between 90% and 5% of peak grip force as measured by computerised myometry, averaged over 3 trials Distance walked after 2 minutes during the 6-Minute Walk Test Average manual muscle testing score over 26 muscle groups (bilateral shoulder abductors, elbow flexors, elbow extensors, wrist flexors, wrist extensors, hip flexors, hip abductors, hip extensors, knee extensors, knee flexors, ankle dorsiflexors, ankle plantar flexors, plus neck extensors, and neck flexors) Average quantitative muscle testing score over 14 muscle groups (bilateral shoulder abduction, elbow flexion, elbow extension, knee flexion, knee extension, ankle dorsiflexion, and hand grip) using the Quantitative Muscle Assessment system, expressed as a percentage of the strength that would be predicted for a healthy person of the same age, sex, and height Total lean body mass measured by dual-energy X-ray absorptiometry Forced vital capacity (sitting and supine; percent normal) Times to go 30 feet, ascend 4 steps, descend 4 steps, go from sitting to standing, and go from sitting to standing 10 times Purdue Pegboard score Jebsen-Taylor hand function test score Upper and lower extremity functional indices Brief Pain Inventory score Epworth Sleepiness Scale SF-36 Physical and Mental Component Summaries INQoL scores Myotonic Dystrophy Health Index scores

Heatwole 2021 *(Continued)*

	Irritable Bowel Syndrome Impact Scale total score Gastrointestinal Symptom Rating Scale total score Time to swallow 100 mL of water Video hand opening times (average times to extend the right third and first digits after 4 seconds of maximum handgrip contraction on a 1-inch diameter dowel rod) Myotonia Visual Analogue Scale
Funding	FDA; TEVA
Conflicts of interest among principal investigators	"Dr. Heatwole receives royalties for the use of multiple disease specific instruments; has provided consultation to Biogen Idec, Ionis Pharmaceuticals, aTyr Pharma, AMO Pharma, Acceleron Pharma, Cytokinetics, Expansion Therapeutics, Harmony Biosciences, Regeneron Pharmaceuticals, Astellas Pharmaceuticals, AveXis, Recursion Pharmaceuticals, and the Marigold Foundation; and receives grant support from Duchenne UK, Parent Project Muscular Dystrophy, Recursion Pharmaceuticals, the National Institute of Neurologic Disorders and Stroke, the Muscular Dystrophy Association, the Friedreich's Ataxia Research Alliance, Cure Spinal Muscular Atrophy, and the Amyotrophic Lateral Sclerosis Association. Dr. Johnson has served as a consultant for AMO Pharma; Asklepios Bio- Pharmaceutical, Inc (AskBio); AveXis, Inc; Dyne Therapeutics; Fulcrum Therapeutics; ML Bio; and Vertex Pharmaceuticals Incorporated and has received personal compensation for speaking engagements from Sarepta Therapeutics and Strongbridge Biopharma plc. Dr Johnson receives research/grant support from AMO Pharma; AveXis, Inc; the Coalition to Cure Calpain 3; CSL Behring; Fulcrum Therapeutics; the Muscular Dystrophy Association; the Myotonic Dystrophy Foundation; the National Institute of Neurologic Disorders and Stroke (K23NS091511-05; R01NS104010-01); Sarepta Therapeutics; and the US Food and Drug Administration (1RO1FD006071-02). Dr Johnson receives publishing royalties from the Charcot-Marie-Tooth Health Index and the Congenital and Childhood Myotonic Dystrophy Health Index. Dr. McDermott has received research support from NIH, FDA, SMA Foundation, Cure SMA, and PTC Therapeutics; served as a consultant for Fulcrum Therapeutics."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Clear description of generation – independent.
Allocation concealment (selection bias)	Low risk	Random sequence generation performed by an independent biostatistics programmer and randomisation performed centrally via a web application.
Blinding of participants and personnel (performance bias)	Low risk	Quadruple blinding.
Blinding of outcome assessment (detection bias)	Low risk	Quadruple blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The statistical analyses included all randomised participants, as randomised, who had ≥ 1 postbaseline evaluation (modified intention to treat approach).
Selective reporting (reporting bias)	High risk	Results for secondary outcome measures including hand grip myotonia for 3 participants in the placebo group were not reported or clearly accounted for. Given the prespecified (modified) intention to treat approach, we judge that these omissions are likely due to selective reporting.

Heatwole 2021 *(Continued)*

Other bias	Low risk	None.

Kratz 1986

Study characteristics	
Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in Washington (DC), USA Treatment period: not stated. Total duration: unclear Results presented as number of participants who improved. No insights in data No washout period
Participants	6 participants with no withdrawals 4 participants with myotonic dystrophy and 2 with myotonia congenita Number of males, females, mean age, and inclusion/exclusion criteria not reported
Interventions	Mexiletine in doses up to 600 mg/day
Outcomes	Grip strength. Relaxation time after making a fist, at room temperature and after the hand in ice water for 1 minute Length of myotonic discharges
Funding	Not reported in text
Conflicts of interest among principal investigators	Not reported in text
Notes	Just a short abstract. Heterogeneous patient population: DM1 and myotonia congenita

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear, not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, not stated.

Kratz 1986 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	High risk	Results presented as number of participants who improved. No insights in data.
Other bias	High risk	No washout period.

Kwiecinski 1992

Study characteristics	
Methods	Randomised, single-blind study. At beginning a cross-over trial of phenytoin and placebo. Afterwards, randomisation for disopyramide, tocainide, or mexiletine. Methods of randomisation: not stated Single centre in Poland Treatment period: 4 weeks Total duration: unclear Results for the cross-over part of the study presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arms not stated. Overall results presented as outcome measures after 4 weeks of treatment.
Participants	30 participants with 2 withdrawals 9 participants with myotonic dystrophy, 9 with dominant myotonia congenita, and 12 with recessive myotonia congenita 22 males, 8 females Mean age: 31.8 years (SD not stated) Inclusion criteria: accepted clinical criteria and EMG characteristics for different diseases Exclusion criteria: none stated
Interventions	Phenytoin 400 mg/day for 2 weeks and 600 mg/day for the last 2 weeks Disopyramide 300 mg/day for 2 weeks and 600 mg/day for the last 2 weeks Mexiletine 400 mg/day for 2 weeks and 600 mg/day for the last 2 weeks Tocainide 800 mg/day for 2 weeks and 1200 mg/day for the last 2 weeks Comparison treatment placebo
Outcomes	Time needed to open eyes maximally after closure (lid myotonia) Time needed to open hand after firm closure (Hand opening) Time needed to climb 10 stairs (Stairtest) EMG relaxation time (after-discharge) Subjective responses

Kwiecinski 1992 *(Continued)*

	Each test was repeated 3 times at intervals of ≥ 10 minutes. The mean value from 3 such measurements was taken as the time value for each test.
Funding	Not reported in text
Conflicts of interest among principal investigators	Not reported in text
Notes	It is conspicuous that the sum of the number of participants in the different treatment groups of the randomisation part of the study exceeded the total number of included participants. Outcomes were not measured in all participants (no reasons given). Heterogeneous patient population: DM1 and myotonia congenita.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	High risk	Single blind. Observers were not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Single blind. Observers were not blinded but unclear if outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 dropouts and not all participants were measured for all outcomes.
Selective reporting (reporting bias)	High risk	Data reported were incomplete. It seems that not all outcomes were measured for all participants.
Other bias	High risk	No washout period in cross-over part of the study.

Lewis 1966

Study characteristics

Methods	Randomised, double-blind cross-over study Randomisation arbitrarily by secretary Single centre in UK Treatment period: 3 weeks Total duration: 6 weeks

Lewis 1966 *(Continued)*

	Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arm stated.
Participants	20 patients and 13 controls 19 patients with myotonic dystrophy and 1 with myotonia congenita Number of males and females not stated Mean age not stated Inclusion criteria: none stated Exclusion criteria: none stated
Interventions	Diazepam 5 mg twice daily to 4 times daily Comparison treatment placebo
Outcomes	Relaxation time with electroencephalogram surface electrodes on right forearm after 5 seconds of maximum voluntary contraction. Value was the mean of 3 measurements Accurate progress notes with specific on grasp myotonia, percussion myotonia, and toxic effects medication
Funding	Not reported in text
Conflicts of interest among principal investigators	Not reported in text
Notes	Evidence of placebo effect; research into placebo tablets pointed out that they contained quinine sulphate 0.5 mg per tablet. Heterogeneous patient population: DM1 and myotonia congenita.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of sequence generation not stated.
Allocation concealment (selection bias)	High risk	Quote: "Randomisation arbitrarily by secretary." Comment: probably not done.
Blinding of participants and personnel (performance bias)	Unclear risk	Methods of blinding not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Methods of blinding not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Twenty patients were seen and examined, only 11 fully completed the six-week, double-blind, crossover study."
Selective reporting (reporting bias)	High risk	Results first arm not stated.

Lewis 1966 *(Continued)*

Other bias	High risk	Placebo effect; research into placebo tablets pointed out that they contain quinine and no washout period.

Leyburn 1959

Study characteristics	
Methods	Randomised, double-blind cross-over study Randomisation by statistician Single centre in UK Treatment period: 3 weeks Total duration: 12 weeks Results presented as individual data for different interventions and as combined data for treatment arms and placebo arms. No washout period. Results first arm not stated.
Participants	20 participants with 4 withdrawals 16 participants with myotonic dystrophy and 4 with myotonia congenita 9 males, 11 females Mean age not stated Inclusion criteria: none stated Exclusion criteria: none stated
Interventions	Quinine (5 grain sugar-coated tablets): 5 grains twice daily first week and 5 grains 3 times daily second and third week Procainamide (0.25 g tablets): 0.5 g 4 times daily first week, 0.75 g 4 times daily second week and 1.0 g 4 times daily third week Prednisone (5 mg tablets): 10 mg twice daily first throughout the 3-week period Comparison treatment placebo
Outcomes	Objective myotonia by measuring 3 times the after-discharge with EMG and by measuring 3 times clinical relaxation time. The result was the average of all 6 measurements. Subjective opinion
Funding	Not reported in text
Conflicts of interest among principal investigators	Not reported in text
Notes	Heterogeneous patient population: DM1 and myotonia congenita.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Leyburn 1959 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Every patient received each of the drugs used, in turn, the order in which these were to be given having been planned in random manner by a statistician." Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Random manner by statistician." Comment: probably done.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study was carried out under "double-blinded" rules, whereby neither the patient nor the doctor who assessed his myotonia at each visit knew which drug was being used at any time."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The study was carried out under "double-blinded" rules, whereby neither the patient nor the doctor who assessed his myotonia at each visit knew which drug was being used at any time."
Incomplete outcome data (attrition bias) All outcomes	High risk	3 dropouts.
Selective reporting (reporting bias)	High risk	Results first arm not stated.
Other bias	High risk	No washout period.

Logigian 2010a

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled cross-over trial Computer-generated randomisation Single centre in Rochester, New York, USA Treatment period: 7 weeks Total duration: 14 weeks (excluding the washout period) Results presented as combined data from both active treatment arms and both placebo arms. Results first arms not stated. 4–8 weeks' washout period. Participants were required to wait ≥ 8 weeks after the end of the first trial to enrol the second trial (Logigian 2010a; Logigian 2010b).
Participants	20 in the first and 20 in the second trial; 10 participants enroled in both trials (Logigian 2010a; Logigian 2010b) 30 participants with DM1 12 males, 8 females Mean age: 46.2 (SD 9.0) years Inclusion criteria: aged 18–80 years, walking independently 15 feet, sufficient finger flexor strength to grasp a handle, standard clinical criteria for the presence of myotonia = time for fingers to fully uncurl following maximal hand grip estimated by visual inspection to be ≥ 3 seconds or percussion myoto-

Logigian 2010a *(Continued)*

	nia in wrist extensor and thenar muscles, satisfied clinical criteria for DM1, and genetic confirmation of DM1 Exclusion criteria: unable to give informed consent, pregnant, lactating, taking medication known to affect myotonia, coexisting neuromuscular disease, another serious medical illness including second- or third-degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmia, history of cardiac arrhythmia requiring medication, congestive heart failure, symptomatic cardiomyopathy, or symptomatic coronary artery disease
Interventions	Mexiletine 150 mg 3 times daily The dosage was titrated so that 3 times daily dosing was reached by day 7 of each treatment period. Medication was tapered over 6 days after the completion of each treatment period. Comparison treatment placebo
Outcomes	Primary measure of myotonia was time for isometric grip force to relax from 90% to 5% of peak force after a 3-second maximum grip contraction. Secondary outcomes were time for isometric grip force to relax from 90% to 10% and 50% to 5%.
Funding	Study funding: this work comes from the University of Rochester Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (NIH/NS048843) and Clinical Research Center (NIH/NCRR MO1 RR00044) with support from the Food and Drug Administration (FD-R- 001662). The work was also supported by the Saunders Family Neuromuscular Research Fund and NIH (AR49077).
Conflicts of interest among principal investigators	Dr Logigian serves on the editorial board of Muscle and Nerve. Mr Martens and Mr Moxley report no disclosures. Dr McDermott has received honoraria from the Michael J. Fox Foundation; has served as a consultant to the New York State Department of Health, the American Epilepsy Society, the Michael J. Fox Foundation, and Teva Pharmaceutical Industries Ltd.; has received research support from Medivation, Inc., Boehringer Ingelheim, NeuroSearch Sweden AB, and Forest Laboratories, Inc.; and receives research support from the NIH (NS42372 [Co-I], HD44430 [Co-I], DE16280 [Co-I], NS52619 [PI], NS45686 [Co-I], NS46487 [Co-I], NS50095 [Co-I], NS49639 [Co-I], AR52274 [Co-I], NS50573 [Co-I], HL80107 [Co-I], RR24160 [Co-I], NS58259 [Co-I], and NS48843 [Co-I]), the US Food and Drug Administration, the Michael J. Fox Foundation, the SMA Foundation, and from the Muscular Dystrophy Association. Ms Dilek, Dr Wiegner, Dr Pearson, Ms Barbieri, and Ms Annis report no disclosures. Dr Thornton receives research support from the NIH (AR046806 [PI], AR049077 [PI], AR48143 [PI], and U54NS48843 [Co-I]), and from the Muscular Dystrophy Association. Dr. Moxley serves on scientific advisory boards for the NIH, the CDC, the Myotonic Dystrophy Foundation, Asklepios BioPharmaceutical, Inc., Acceleron Pharma, Wyeth, and Insmed Inc.; and receives research support from the FDA, the NIH (NIAMS N01-AR-0-2250 [PI], NCRR 5 MO1 RR00044 [Co-Director], NIAMS R01 AR49077 [Co-I], 9 U54NS48843 [PI], NCRR 1UL 1RR02416002 [Co-Director], N01-AR-5-2274 [PI], 1 R13 NS066630-01 [PI], and NIAMS 2 R01 AR049077 [Co-I]), the Saunders Family Foundation, and from the Muscular Dystrophy Association.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned in each trial to 1 of 2 treatment sequences: mexiletine/placebo or placebo/mexiletine. The computer-generated randomisation plans including blocking to ensure approximate balance between the 2 treatments sequences."
Allocation concealment (selection bias)	Low risk	Quote: "A programmer in the Department of Biostatistics generated the randomisation plans and sent them to the pharmacy where drug packaging and labeling took place. All drug was labeled with a participant ID number. Only the biostatistics programmer and the pharmacist had access to the treatment assignments. Drug was assigned sequentially. The study coordinator was re-

Logigian 2010a *(Continued)*

		quired to check all baseline forms for completeness and verify eligibility criteria before calling the pharmacy to officially randomise a participant."
Blinding of participants and personnel (performance bias)	Low risk	Double blind. Quote: "Active and placebo medication were re-encapsulated in gelatin capsules by the pharmacy to facilitate blinding."
Blinding of outcome assessment (detection bias)	Low risk	Double blind. Quote: "Active and placebo medication were re-encapsulated in gelatin capsules by the pharmacy to facilitate blinding."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals, well addressed.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Washout period.

Logigian 2010b

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled cross-over trial Computer-generated randomisation Single centre in Rochester, New York, USA Treatment period: 7 weeks Total duration: 14 weeks (excluding the washout period) Results presented as combined data from both active treatment arms and both placebo arms. Results first arms not stated. 4–8 weeks' washout period. Participants were required to wait ≥ 8 weeks after the end of the first trial to enrol in the second trial (Logigian 2010a; Logigian 2010b).
Participants	20 in the first and 20 in the second trial; 10 participants enroled in both trials (Logigian 2010a; Logigian 2010b) 30 participants with DM1 13 males, 7 females Mean age: 42.6 (SD 8.6) years Inclusion criteria: aged 18–80, walking independently 15 feet, sufficient finger flexor strength to grasp a handle, standard clinical criteria for the presence of myotonia = time for fingers to fully uncurl following maximal hand grip estimated by visual inspection to be ≥ 3 seconds or percussion myotonia in wrist extensor and thenar muscles, satisfied clinical criteria for DM1, and genetic confirmation of DM1 Exclusion criteria: unable to give informed consent, pregnant, lactating, taking medication known to affect myotonia, coexisting neuromuscular disease, another serious medical illness including second- or third-degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmia, history of cardiac

Logigian 2010b *(Continued)*

	arrhythmia requiring medication, congestive heart failure, symptomatic cardiomyopathy, or symptomatic coronary artery disease.
Interventions	Mexiletine 200 mg 3 times daily The dosage was titrated so that 3 times daily dosing was reached by day 7 of each treatment period. Medication was tapered over 6 days after the completion of each treatment period Comparison treatment placebo
Outcomes	Primary measure of myotonia was time for isometric grip force to relax from 90% to 5% of peak force after a 3-second maximum grip contraction Secondary outcomes were time for isometric grip force to relax from 90% to 10% and 50% to 5%
Funding	Study funding: this work comes from the University of Rochester Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (NIH/NS048843) and Clinical Research Center (NIH/NCRR MO1 RR00044) with support from the Food and Drug Administration (FD-R- 001662). The work was also supported by the Saunders Family Neuromuscular Research Fund and NIH (AR49077).
Conflicts of interest among principal investigators	Dr Logigian serves on the editorial board of Muscle and Nerve. Mr Martens and Mr Moxley report no disclosures. Dr McDermott has received honoraria from the Michael J. Fox Foundation; has served as a consultant to the New York State Department of Health, the American Epilepsy Society, the Michael J. Fox Foundation, and Teva Pharmaceutical Industries Ltd.; has received research support from Medivation, Inc., Boehringer Ingelheim, NeuroSearch Sweden AB, and Forest Laboratories, Inc.; and receives research support from the NIH (NS42372 [Co-I], HD44430 [Co-I], DE16280 [Co-I], NS52619 [PI], NS45686 [Co-I], NS46487 [Co-I], NS50095 [Co-I], NS49639 [Co-I], AR52274 [Co-I], NS50573 [Co-I], HL80107 [Co-I], RR24160 [Co-I], NS58259 [Co-I], and NS48843 [Co-I]), the US Food and Drug Administration, the Michael J. Fox Foundation, the SMA Foundation, and from the Muscular Dystrophy Association. Ms Dilek, Dr Wiegner, Dr Pearson, Ms Barbieri, and Ms Annis report no disclosures. Dr Thornton receives research support from the NIH (AR046806 [PI], AR049077 [PI], AR48143 [PI], and U54NS48843 [Co-I]), and from the Muscular Dystrophy Association. Dr Moxley serves on scientific advisory boards for the NIH, the CDC, the Myotonic Dystrophy Foundation, Asklepios BioPharmaceutical, Inc., Acceleron Pharma, Wyeth, and Insmed Inc.; and receives research support from the FDA, the NIH (NIAMS N01-AR-0-2250 [PI], NCRR 5 MO1 RR00044 [Co-Director], NIAMS R01 AR49077 [Co-I], 9 U54NS48843 [PI], NCRR 1UL 1RR02416002 [Co-Director], N01-AR-5-2274 [PI], 1 R13 NS066630-01 [PI], and NIAMS 2 R01 AR049077 [Co-I]), the Saunders Family Foundation, and from the Muscular Dystrophy Association.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned in each trial to 1 of 2 treatment sequences: mexiletine/placebo or placebo/mexiletine. The computer-generated randomisation plans including blocking to ensure approximate balance between the 2 treatments sequences."
Allocation concealment (selection bias)	Low risk	Quote: "A programmer in the Department of Biostatistics generated the randomisation plans and sent them to the pharmacy where drug packaging and labeling took place. All drug was labeled with a participant ID number. Only the biostatistics programmer and the pharmacist had access to the treatment assignments. Drug was assigned sequentially. The study coordinator was required to check all baseline forms for completeness and verify eligibility criteria before calling the pharmacy to officially randomise a participant."
Blinding of participants and personnel (performance bias)	Low risk	Double blind.

Logigian 2010b *(Continued)*

		Quote: "Active and placebo medication were re-encapsulated in gelatin capsules by the pharmacy to facilitate blinding."
Blinding of outcome assessment (detection bias)	Low risk	Double blind. Quote: "Active and placebo medication were re-encapsulated in gelatin capsules by the pharmacy to facilitate blinding."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals, well addressed.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	Washout period.

Munsat 1967

Study characteristics	
Methods	Randomised, double-blind cross-over study Method of randomisation: not stated Single centre in Los Angeles, USA Treatment period: 3 weeks Total duration: 9 weeks Results presented as combined data from 4 active treatment arms and both placebo arms. No washout period. Results for first arm not stated.
Participants	9 participants without withdrawals 7 participants with myotonic dystrophy and 2 with myotonia congenita Number of males and females not stated Mean age: not stated Inclusion criteria: accepted clinical criteria, electromyography and muscle biopsy. Selected on the basis of intelligence and capability of being examined weekly and presented a spectrum of clinical involvement Exclusion criteria: none stated
Interventions	Diphenylhydantoin 100 mg twice daily first week, 3 times daily second week, and 4 times daily third week Procainamide 1 g twice daily first week, 3 times daily second week, and 4 times daily third week Comparison treatment placebo
Outcomes	Ergographic evaluation of hand grasp after 5 seconds of maximum voluntary contraction Subjective report regarding efficacy or toxicity or both Repeated ECG utilising standard leads

Munsat 1967 *(Continued)*

Funding	Not reported in text
Conflicts of interest among principal investigators	Not reported in text
Notes	Researcher could recognise medicine of participants by type of adverse events Heterogeneous patient population: DM1 and myotonia congenita

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A crossover technique was used so that the patients received every compound in a random manner."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The medications were packaged in identical capsules and given in the same number."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The medications were packaged in identical capsules and given in the same number."
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	High risk	Results for first arm not given.
Other bias	High risk	No washout period.

Statland 2012

Study characteristics

Methods	Randomised, double-blind, cross-over study Setting: 7 centres in 4 countries Number of participants: 59 62 participants recruited, 3 not eligible. 1 had a prolonged QTc at screening visit, 1 had an elevated transaminase, and 1 had no clinical myotonia on examination. 59 participants were randomised to receive study medication or placebo. Age: 16–68 years; mean age 42.9 Sex: 33 men, 26 women Mexiletine first: 13 males, 16 females Placebo first: 20 males, 10 females

Statland 2012 *(Continued)*

	Race/ethnicity: majority white (57/59) and non-Hispanic (46/59) Mexiletine first: 28 white, 1 not white Placebo first: 29 white, 0 not white
Participants	59 people with genetically confirmed NDM or with clinical features of NDM but negative myotonic dystrophy DNA testing Inclusion criteria: aged ≥ 16 years, had clinical symptoms or signs of NDM, and myotonic potentials on electromyography Participants were either enroled in the CINCH NDM Natural History Study, or a new patient with genetically confirmed NDM, or with clinical features of NDM but negative myotonic dystrophy DNA testing People taking antimyotonic agents were required to discontinue medications for a washout period equal to 7 times the half-life of elimination prior to their baseline visit. Exclusion criteria: specific contraindications to taking mexiletine (cardiac conduction defects, hepatic or renal disease, or heart failure)
Interventions	Mexiletine 200 mg capsules 3 times daily or placebo 200 mg capsules 3 times daily for 4 weeks. After a 1-week washout period, they were placed on the opposite intervention for 4 weeks Placebo
Outcomes	**Primary outcome** Endpoint defined as the severity score of stiffness reported by participants during the 3rd and 4th week of each treatment period via the IVR. Participants called in to report symptom severity on a 1–9 scale, 1 being minimal and 9 the worst ever experienced (no symptom = 0). **Secondary outcomes** Participant-assessed pain, weakness, and tiredness as measured by the IVR from daily calls made over the last 2 weeks of each period Clinical myotonia bedside assessment: participants were asked to squeeze their eyes closed for 5 seconds then rapidly open them; and make a tight fist for 5 seconds then rapidly open. 5 trials of each manoeuvre were performed in sequence at each visit and the time measured on a stopwatch. A quantitative measure of handgrip myotonia was obtained using a commercially available grip dynamometer and computerised capture system. Maximum voluntary contractions following forced right-hand grip were recorded and the time to relax from 90% to 5% of maximal force was determined using automated analysis software. Maximal postexercise decrement in compound muscle action potential after short and long exercise Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti minimi and right tibialis anterior SF-36 and the INQoL questionnaire for neuromuscular disorders. The INQoL is comprised of 10 sections (muscle locking, weakness, pain, fatigue, activities, social relationships, independence, emotions, body image, and effects of treatment) and a summary quality of life score.
Funding	This study was supported by the FDA Orphan Products Division- FDA-OPD RO1 FD 003454 and the National Center for Research Resources and the National Institutes of Health through Grant Number U54 NS059065-05S1. Additional funding was provided in part by the University of Kansas Medical Center CTSA grant UL1 RR 033179, the University of Rochester CTSA grant UL1 RR 024160, University College London MRC Centre grant G0601943, and the University of Texas Southwestern CTSA grant UL1 RR 024982 NCRR/NIH. Dr Rayan is an MRC Clinical Training Fellow. Dr Statland is funded by the NIH Experimental Therapeutics in Neurological Disorders grant # T32 NS07338-20.

Statland 2012 *(Continued)*

	The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Conflicts of interest among principal investigators	The authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Venance reports receiving reimbursement for travel from Genzyme and royalties from Wiley Publishing for her role as co-editor Neurology in Practice: Neuromuscular Disorders. Dr Meola is supported in part by AFM. Dr Griggs serves as Chair of Executive Committee of the Muscle Study Group, which receives support from pharmaceutical companies; has served on scientific advisory boards for The National Hospital Queen Square and PTC Therapeutics, Inc.; serves on the editorial boards of NeuroTherapeutics and Current Treatment Opinions in Neurology; receives royalties from the publication of Andreoli and Carpenter's Cecil Essentials of Medicine, Eighth Edition (W.B. Saunders Company, 2000, 2004, 2007, and 2010) and Cecil Textbook of Medicine, 24th Edition (Saunders, 2000, 2004, 2008, and 2010 [in press]); and has received research support from TaroPharma. Dr Barohn receives support from Grifols and Genzyme Speakers Bureau, and is a consultant for Pfizer, MedImmune, Novartis, and NuFactor. Role of the sponsor: the funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned the order of the 2 treatments in a 1:1 ratio, stratified by institution. Randomisation was done centrally at the Data Management Coordinating Center (University of South Florida) using a computer-generated permuted block structure, initially with a block size of 4 then towards the end of the trial, switching to a block size of 2.
Allocation concealment (selection bias)	Low risk	Participants, physicians, and evaluators were blinded to medication assignment. Each participant was assigned a 'Kit' number. In this kit, there were only 2 bottles of medication ('A' for period 1 and 'B' for period 2). Only 1 bottle was dispensed at a time.
Blinding of participants and personnel (performance bias)	Low risk	Participants, physicians, and evaluators were blinded to medication assignment.
Blinding of outcome assessment (detection bias)	Low risk	Participants, physicians, and evaluators were blinded to medication assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Mexiletine first** 29: 4 dropouts in first period (1 migraine, 1 gastrointestinal discomfort, 1 noncompliance with visits, 1 made no calls to IVR in either period). 2 withdrew in 2nd period – no calls to IVR. 23 completed study, 28 analysed (1 excluded from analysis as failure to call IVR during either period). **Placebo first** 30 participants – 1 withdrew in first period – made no calls to IVR in either period. 29 completed study, 29 analysed, 1 excluded from study – failure to make any calls to IVR during either period.

Statland 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

Stunnenberg 2018

Study characteristics	
Methods	Randomised controlled trial Age: > 18 years; mean: 43.4 (SD 15.2) years Number of participants: 30 27 completed the study, 4 completed 2 treatment sets and 3 dropped out (1 because of a serious adverse event) Sex: 22% men Inclusion criteria: aged ≥ 18 years; genetically confirmed diagnosis of NDMs Exclusion criteria: inability or unwillingness to provide informed consent; other neurological conditions that might affect the assessment of the study measurements; genetic confirmed DM1 (CTG > 50 repeats), or DM2; existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbances (such as second degree AV block, third degree AV block, or prolonged QT interval > 500 ms or QRS duration > 150 ms); current use of the following antiarrhythmic medication for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone, or mexiletine; pregnant or lactating; currently on medications for myotonia such as phenytoin and flecainide acetate within 5 days of enrolment, carbamazepine and mexiletine within 3 days of enrolment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrolment; renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders.
Participants	30 adults with non-dystrophic myotonia, with genetically confirmed diagnosis
Interventions	Mexiletine 600 mg daily Placebo
Outcomes	**Primary outcome** Mean daily self-reported stiffness severity score reported with an IVR Diary **Secondary outcomes** Mean daily self-reported (using the IVR) severity scores for pain, weakness, and tiredness INQoL questionnaire composite score (0–100 scale; a higher score indicates greater disease severity) SF-36 (Dutch version) Mental and Physical Component Scores (both 0–100 scales; lower score indicates greater disease severity) First, fifth, and mean of 5 attempts of myotonic bedside tests: eyelid closure and handgrip muscle relaxation times after forceful muscle contraction for 5 seconds Timed Up and Go test, which measures the time in which the participant rises from a chair, walks 3 m, turns around, walks back, and sits down again, at a self-selected speed Blood plasma levels of mexiletine

Stunnenberg 2018 *(Continued)*

	Needle EMG
Funding	Quote "*This study was funded by ZonMw, The Netherlands Organisation for Health Research and Development (ZonMw project 152002029). Dr Statland's work on this project was supported by a Clinical and Translational Science Awards grant awarded to the University of Kansas Medical Center for Frontiers: University of Kansas Clinical and Translational Science Institute (KL2TR000119). Dr Mathews holds a National Institute for Health Research (NIHR) rare disease TRC postdoctoral fellowship, which is supported via the University College London Hospitals NIHR Biomedical Research Centre.*"
Conflicts of interest among principal investigators	Quote: "Dr Statland reported receiving grants from the National Institute of Neurological Disorders and Stroke and the FSH Society and receiving personal fees from Acceleron, Sarepta, Fulcrum, and PTC. Dr Griggs reported receiving grants (during the conduct of the study) from the National Institutes of Health, Muscular Dystrophy Association, and Parent Project for Muscular Dystrophy and receiving personal fees from Strongbridge Pharmaceuticals, Sarepta Pharmaceuticals, Marathon Pharmaceuticals, and Stealth Pharmaceuticals. Dr Matthews reported receiving compensation, after the research and manuscript were completed and submitted, for attending a scientific advisory meeting at the request of LUPIN pharmaceuticals, which is seeking European Medicines Agency approval for mexiletine. Dr van Engelen reported receiving grants from European Union's Horizon 2020 research and innovation programme (Murab), European FP7 programme (OPTIMISTIC), Association Francaise contre les Myopathies, Global FSH, The Netherlands Organisation for Health Research and Development (ZonMw), Prinses Beatrix Spierfonds, Stiching Spieren voor Spieren, Dutch FSHD Foundation, and The Netherlands Organisation for Scientific Research and receiving personal fees from Fulcrum. No other disclosures were reported."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described – computer based.
Allocation concealment (selection bias)	Low risk	Described, independent statistician prepared randomisation sequence and pharmacy prepared allocated treatments.
Blinding of participants and personnel (performance bias)	Low risk	Described – blinded.
Blinding of outcome assessment (detection bias)	Low risk	Low risk.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants who completed ≥ 1 treatment period were included in analyses, 3 participants excluded.
Selective reporting (reporting bias)	Unclear risk	Described primary outcomes, some secondary outcomes not reported.
Other bias	Low risk	None.

Vicart 2021

Study characteristics

Methods	Double-blind, placebo-controlled, cross-over randomised controlled trial

Vicart 2021 *(Continued)*

	Age: 18–65 years; mean 43 (SD 11.4) years Number of participants: 25 (initially 26, 1 person dropped out before any study medication was taken. Modified intention to treat: 25 (13 myotonia congenita and paramyotonia congenita, 12 PMC)) Sex: 17 (68%) males Settings: multicentre in France (6 centres) Inclusion criteria: genetically definite myotonia congenita and paramyotonia congenita; adults aged 18–65 years, who were able to comply with the study conditions; experienced myotonic symptoms severe enough to justify treatment (severity based on: clinical criteria: myotonia was considered severe if it involved at least 2 segments (upper limb, lower limb or face)); disabling criteria: myotonia was considered severe if participants noticed impacts on ≥ 3 of 7 daily activities (talking, writing, feeding, hygiene, getting dressed, walking, climbing stairs); were drug-naïve or those who were receiving mexiletine at an effective dosage and who agreed to stop treatment ≥ 4 days before inclusion; non-childbearing potential women (i.e. postmenopausal or surgically sterile) or using a medically accepted contraceptive regimen; normal cardiac examination performed by a cardiologist including ECG and cardiac ultrasound (if not done within 3 months before trial) Exclusion criteria: intercurrent event which could interfere with muscle function (infection, trauma, fracture, etc.); coincidental renal, hepatic, respiratory, thyroid, other neuromuscular disease or heart disease that contraindicated mexiletine or interfered with clinical evaluation; use of any of the following medications that could interfere with muscle function: diuretics, antiepileptics (sodium channel blockers), anti-arrhythmic, corticosteroids, and beta-blockers; allergy to mexiletine
Participants	People with genetically confirmed NDM with myotonia present on clinical assessment, aged 18–65 years
Interventions	Mexiletine Placebo
Outcomes	**Primary outcome** Score of stiffness severity on a self-assessment scale (100-mm Visual Analogue Scale) at 18 days **Secondary outcomes** Standardised EMG CMAP measures after repetitive short exercise test at cold and long exercise test at 18 days Chair test: time needed to stand up from a chair, walk around it, and sit down again at 18 days Severity and disability scale of myotonia to be validated at 18 days Quality of life scale (INQoL) at 18 days Clinical Global Impression – Efficacy index at 18 days Preference for which period and willingness to continue mexiletine
Funding	Study supported by Assistance Publique-Hôpitaux de Paris (AP-HP) and AFM-Téléthon
Conflicts of interest among principal investigators	S Vicart reports serving on scientific advisory boards and being a consultant for Lupin starting after the end of the study. Y Péréon reports personal fees from Lupin, outside the submitted work. B Fontaine reports grants from AFM-Telethon during the conduct of the study. The other authors did not report conflicts of interest.
Notes	
Risk of bias	

Vicart 2021 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described – stratified by diagnosis.
Allocation concealment (selection bias)	Low risk	Described – sequence allocation was concealed from patients and personnel.
Blinding of participants and personnel (performance bias)	Unclear risk	Participants may self-unblind due to nature of study.
Blinding of outcome assessment (detection bias)	Unclear risk	Participants may self-unblind due to nature of study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Described – per-protocol or intention-to-treat analyses.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

CMAP: compound muscle action potential; CTG: cytosine-thymine-guanine; DM1: myotonic dystrophy type 1; DM2: myotonic dystrophy type 2; ECG: electrocardiogram; EMG: electromyographic; INQoL: Individualized Quality of Life; IVR: Interactive Voice Response; NDM: non-dystrophic myotonia; SD: standard deviation; SF-36: 36-item Short Form.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alfonsi 2007	Case study.
Arnold 2017	Non-randomised open study.
Backman 1990	Non-randomised uncontrolled study.
Benstead 1987	Case study.
Birnberger 1975	Non-randomised uncontrolled study.
Brumback 1983	Non-randomised open study.
Chisari 2009	Non-randomised uncontrolled study
Cook 1984	Case study.
Durelli 1982	Non-randomised study.
Garai 1954	Case study.
Geschwind 1955	Case study.
Griggs 1977	Non-randomised study.

Study	Reason for exclusion
Griggs 1978	Non-randomised open study.
Griggs 1989	No myotonia as outcome measure.
Guilleminault 1978	Non-randomised study.
Heatwole 2011	Non-randomised uncontrolled study. No myotonia as outcome measure.
Hughes 1991	Case studies.
Jackson 1994	Case study.
Karli 1974	Case study.
Lorusso 2019	Non-randomised open study.
Matsumura 2004	Non-randomised open study.
Mielke 1985	Non-randomised study.
Milner-Brown 1990	Non-randomised uncontrolled study.
Müller 1980	Non-randomised open study.
Orndahl 1986	Non-randomised study.
Orndahl 1994	No myotonia as outcome measure.
Pendefunda 1974	Case study.
Pénisson-Besnier 2008	No myotonia as outcome measure.
Ricker 1980	Non-randomised open study.
Rüdel 1980	Non-randomised study.
Samaha 1964	Non-randomised study.
Schneider-Gold 2003	No myotonia as outcome measure.
Sechi 1983	Non-randomised study.
Streib 1987	Case study.
Sugino 1998	Non-randomised open study.
Tarnopolsky 2004	No myotonia as outcome measure; only muscle forces, functional measures, and activities of daily living scales.
Vlachopapadopoulou 1995	No myotonia as outcome measure.
Walter 2002	No myotonia as outcome measure.

Characteristics of ongoing studies *[ordered by study ID]*

NCT03692312

Study name	A randomized, double-blind study to evaluate the efficacy and safety of tideglusib versus placebo for the treatment of children and adolescents with congenital myotonic dystrophy (REACH CDM)
Methods	Randomised blinded trial
Participants	56
Interventions	Tineglusib vs placebo
Outcomes	**Primary outcome** Change in Clinician-Completed Congenital DM1 Rating Scale (11-item rating scale completed by the clinician that scores the symptom severity of domains that are clinically relevant in congenital DM1) **Secondary outcomes** Change in Clinical Global Impression – Improvement Scale scores Change in Top 3 Caregiver Concerns Visual Analogue Scale score Caregiver Completed Congenital DM1 Rating Scale Clinical Global Impression – Severity Scale 10-m walk-run test Incidence of adverse events, including serious adverse events, between screening and end of study Incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, vital signs, and bone mineral density) between screening and end of study
Starting date	3 March 2021
Contact information	
Notes	

NCT04622553

Study name	Open-label extension study in paediatric patients who have completed the MEX-NM-301 study
Methods	Open-label extension
Participants	14
Interventions	Mexiletine
Outcomes	**Primary outcome** Long-term safety and tolerability of mexiletine by adverse events Hand relaxation – mean time (in seconds) to relaxation of hand muscles and reduction in relaxation time from the first to the fifth contraction

NCT04622553 *(Continued)*

	Incidence of adverse events of special interest Changes in ECG assessments from baseline, repeated at each study visit Visual Analogue Scale or Faces scale **Secondary outcomes** Mean change in Visual Analogue Scale (aged 8 to < 18 years) or Faces (aged 8 to < 8 years) score for severity of muscle stiffness (if not a primary endpoint) pain, weakness, and fatigue (every 3 months) Mean change in time to open the eyes after forced eye closure as measured on a stopwatch (when eyelid myotonia present) Paediatric Quality of Life score Clinical Global Impression scores (efficacy and tolerability) Myotonia Behaviour Scale scores Timed Up and Go test
Starting date	5 November 2021
Contact information	NikkiAdetoro@lupin.com
Notes	

NCT04624750

Study name	Open label study in adolescents and children with myotonic disorders
Methods	Open-label, multicentre, single arm, interventional study
Participants	14
Interventions	Mexiletine
Outcomes	**Primary outcomes** Number and frequency of adverse events/serious adverse events Incidence of adverse events of special interest Changes in ECG assessments from baseline Efficacy of Namuscla treatment on the clinical outcomes based on the following functional evaluation mean change in Visual Analogue Scale for muscle stiffness Score of handgrip myotonia as quantitatively measured using a commercially available grip dynamometer and computerised capture system. In standardised conditions (i.e. in a room at controlled temperature, after a definite period of rest), maximum voluntary contractions following forced right hand grip will be recorded and the time to relax from 90% to 5% of maximal force will be determined using automated analysis software **Secondary outcomes** Mean change in Visual Analogue Scale score for muscle pain, weakness, and fatigue Mean change in time to open the eyes after forced eye closure as measured on a stopwatch

NCT04624750 *(Continued)*

	Clinical myotonia assessment of clinical change in flexor myotonia
	Timed Up and Go
	Paediatric Quality of Life score
	Clinical Global Impression scores
	Myotonia Behaviour Scale scores
	Faces scale for muscle pain, weakness, and fatigue
	Laboratory measures – potassium, sodium, chloride, calcium
Starting date	3 September 2021
Contact information	NikkiAdetoro@lupin.com
Notes	

NCT05017155

Study name	MExiletine versus lamotrigine in Non-Dystrophic myotonias (MEND)
Methods	Randomised double-blind cross-over trial
Participants	60
Interventions	Mexiletine vs lamotrigine
Outcomes	**Primary outcome**
	Interactive Voice Response Diary score
	Secondary outcomes
	Timed sit to stand
	Fatigue Scale
	Brain Pain Inventory
	36-item Short-Form Health Survey
	Myotonia Behaviour Score
Starting date	12 August 2021
Contact information	v.vivekanandam@ucl.ac.uk
Notes	NCT05017155

NCT05639257

Study name	Treatment of myotonia – lamotrigine versus namuscla

NCT05639257 *(Continued)*

Methods	Randomised cross-over trial
Participants	
Interventions	Lamotrigine versus namuscla (mexiletine)
Outcomes	**Primary outcome** Change in Myotonia Behaviour Scale **Secondary outcomes** Change in eye-myotonia Change in hand-myotonia Change in Time Up and Go test Change in Individualized Neuromuscular Quality of Life Questionnaire Days with adverse effects Change in Side Effect Scale
Starting date	5 December 2022
Contact information	
Notes	

DM1: myotonic dystrophy type 1; ECG: electrocardiogram.

DATA AND ANALYSES

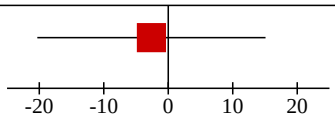
Comparison 1. Mexiletine versus placebo in myotonic dystrophy type 1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Improvement of myotonia: visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2 Relaxation time (seconds, 90% to 5%)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Mexiletine 150 mg 3 times daily	2		Mean Difference (IV, Fixed, 95% CI)	-1.37 [-1.86, -0.87]
1.2.2 Mexiletine 200 mg 3 times daily	1		Mean Difference (IV, Fixed, 95% CI)	-1.36 [-2.09, -0.63]
1.3 Quality of life: 36-item Short Form	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Physical Component Summary (PCS)	1		Mean Difference (IV, Fixed, 95% CI)	-1.40 [-5.56, 2.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Mental Component Summary (MCS)	1		Mean Difference (IV, Fixed, 95% CI)	-1.10 [-6.17, 3.97]
1.4 Quality of life: Individualized Neuromuscular Quality of Life	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: Mexiletine versus placebo in myotonic dystrophy type 1, Outcome 1: Improvement of myotonia: visual analogue scale

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Heatwole 2021[a]	-2.61	9.028181	-2.61 [-20.30 , 15.08]		+ + + + + − +



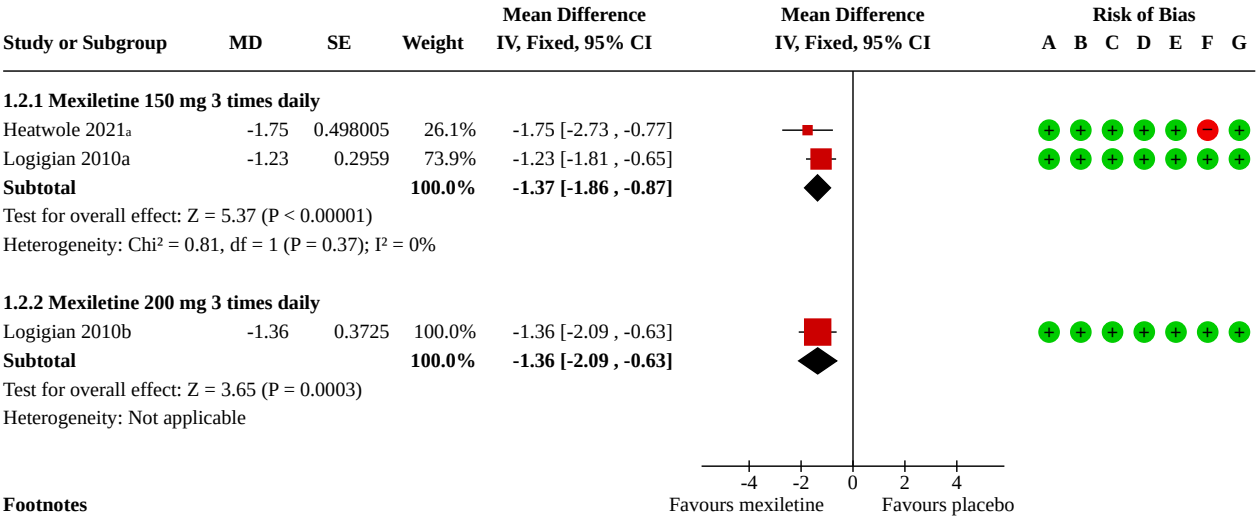
Footnotes

[a]95% CIs of MD are slightly different to those reported in Heatwole 2021 (derived from a repeated measures analysis of covariance model).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Mexiletine versus placebo in myotonic dystrophy type 1, Outcome 2: Relaxation time (seconds, 90% to 5%)



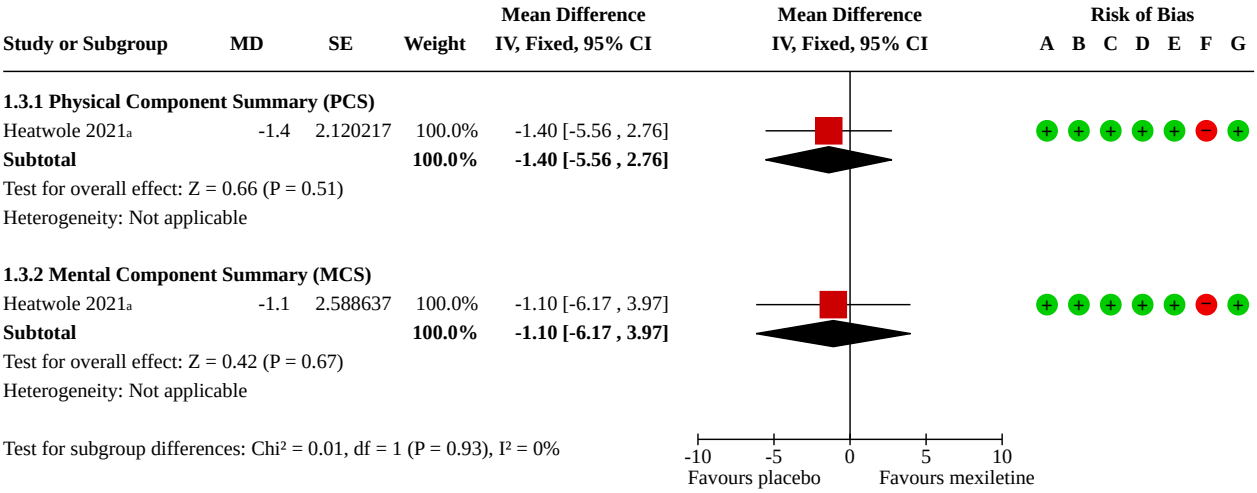
Footnotes

[a]95% CIs of MD are slightly different to those reported in Heatwole 2021 (derived from a repeated measures analysis of covariance model).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Mexiletine versus placebo in myotonic dystrophy type 1, Outcome 3: Quality of life: 36-item Short Form



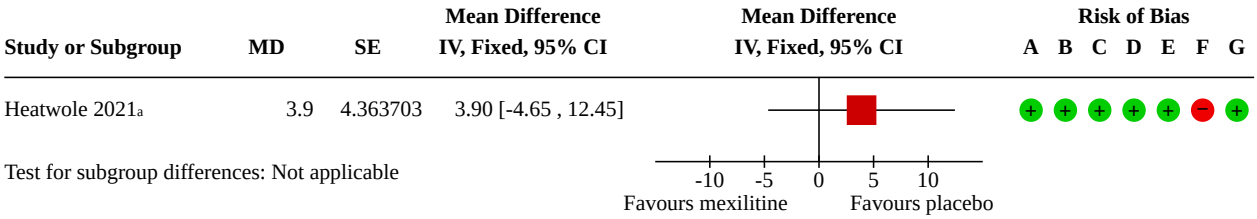
Footnotes

[a]95% CIs of MD are slightly different to those reported in Heatwole 2021 (derived from a repeated measures analysis of covariance model).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Mexiletine versus placebo in myotonic dystrophy type 1, Outcome 4: Quality of life: Individualized Neuromuscular Quality of Life



Footnotes

[a]95% CIs of MD are slightly different to those reported in Heatwole 2021 (derived from a repeated measures analysis of covariance model).

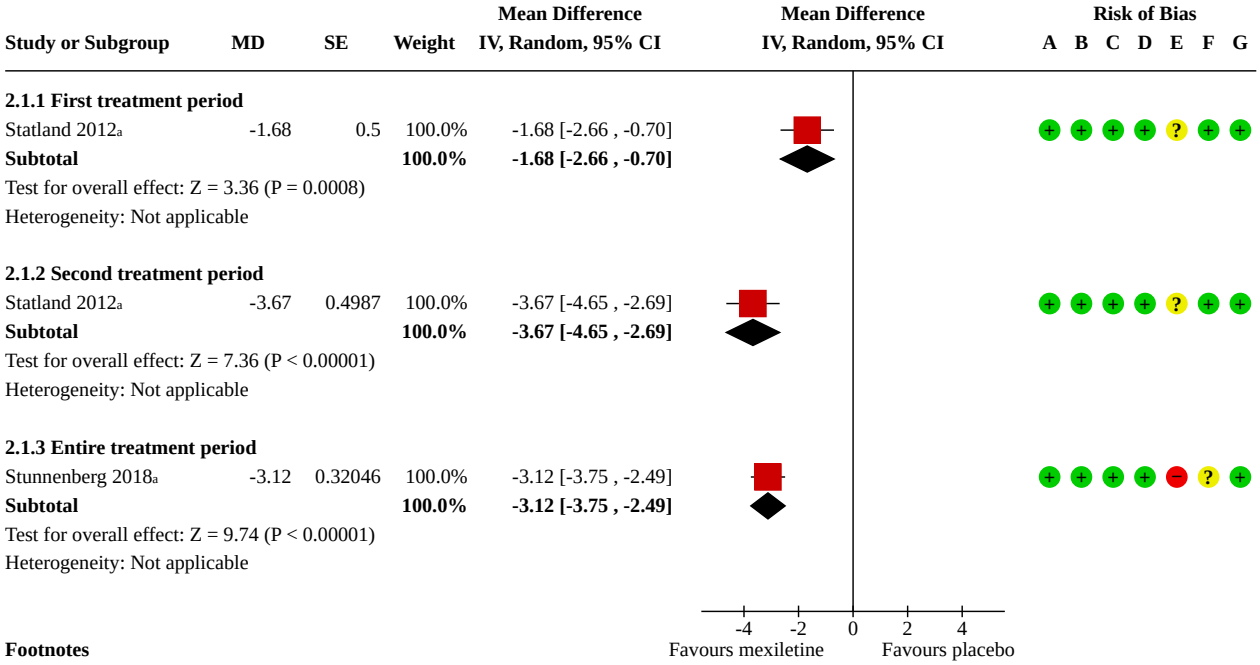
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Mexiletine versus placebo in non-dystrophic myotonias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Improvement of myotonia: stiffness reported on interactive voice response system	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 First treatment period	1		Mean Difference (IV, Random, 95% CI)	-1.68 [-2.66, -0.70]
2.1.2 Second treatment period	1		Mean Difference (IV, Random, 95% CI)	-3.67 [-4.65, -2.69]
2.1.3 Entire treatment period	1		Mean Difference (IV, Random, 95% CI)	-3.12 [-3.75, -2.49]
2.2 Relaxation time (seconds)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 Eye closure	2		Mean Difference (IV, Random, 95% CI)	-1.04 [-2.76, 0.69]
2.2.2 Hand grip	2		Mean Difference (IV, Random, 95% CI)	-0.62 [-1.37, 0.14]
2.2.3 Quantitative hand grip (90% to 5%)	1		Mean Difference (IV, Random, 95% CI)	-0.11 [-0.18, -0.04]
2.3 Electromyographic (EMG) relaxation time	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Needle EMG: right abductor digiti minimi	1		Mean Difference (IV, Fixed, 95% CI)	-0.57 [-0.81, -0.32]
2.3.2 Needle EMG: right tibialis anterior	1		Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.68, -0.25]
2.3.3 Needle EMG: left rectus femoris	1		Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.10, -0.24]
2.4 Quality of life: 36-item Short Form	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Physical Component Score (PCS)	2		Mean Difference (IV, Random, 95% CI)	6.45 [4.32, 8.58]
2.4.2 Mental Component Score (MCS): first treatment period	1		Mean Difference (IV, Random, 95% CI)	-0.35 [-5.75, 5.05]
2.4.3 Mental Component Score (MCS): second treatment period	1		Mean Difference (IV, Random, 95% CI)	10.40 [0.80, 20.00]
2.4.4 Mental Component Score: entire treatment period	1		Mean Difference (IV, Random, 95% CI)	6.78 [1.89, 11.67]
2.5 Quality of life: Individualized Neuromuscular Quality of Life	2		Mean Difference (IV, Random, 95% CI)	-7.35 [-18.44, 3.74]

Analysis 2.1. Comparison 2: Mexiletine versus placebo in non-dystrophic myotonias, Outcome 1: Improvement of myotonia: stiffness reported on interactive voice response system



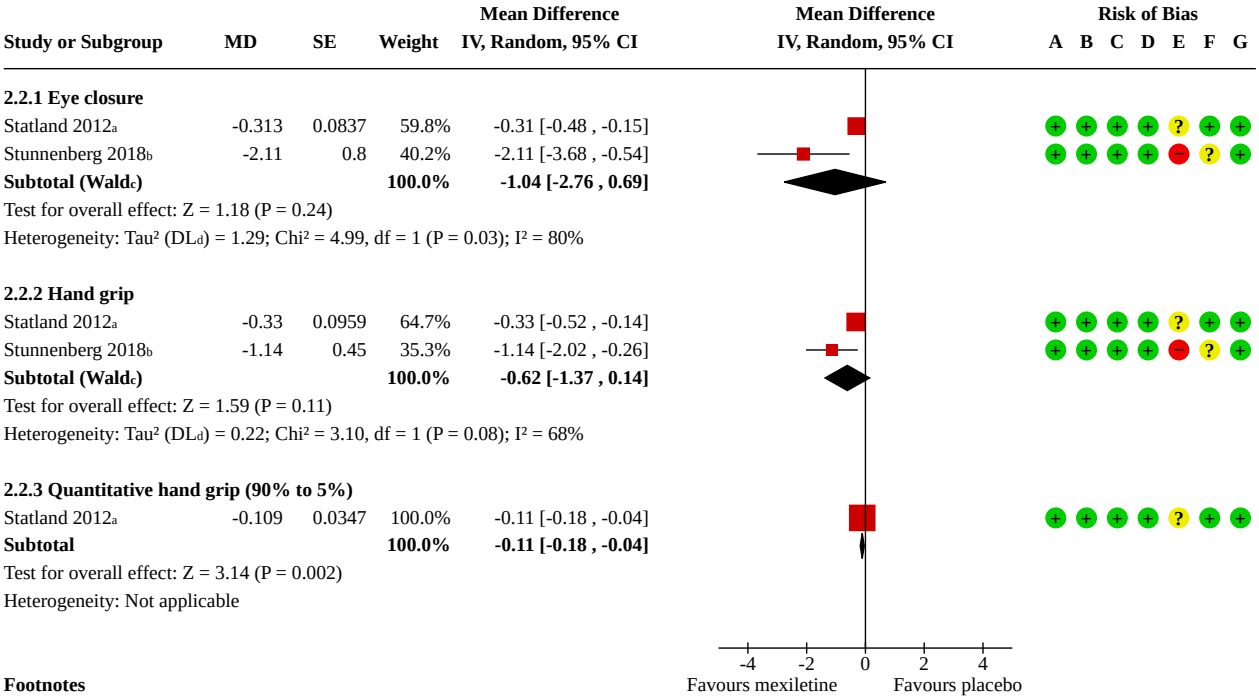
Footnotes

[a]95% CIs of MD are slightly different to those reported in Statland 2012 (derived from a linear mixed-effects model with bootstrap 95% CIs).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Mexiletine versus placebo in non-dystrophic myotonias, Outcome 2: Relaxation time (seconds)



Footnotes

[a]95% CIs of MD are slightly different to those reported in Statland 2012 (derived from a linear mixed-effects model with bootstrap 95% CIs).

[b]95% CIs of MD are slightly different to those reported in Stunnenberg 2018 (derived from a linear mixed-effects model).

[c]CI calculated by Wald-type method.

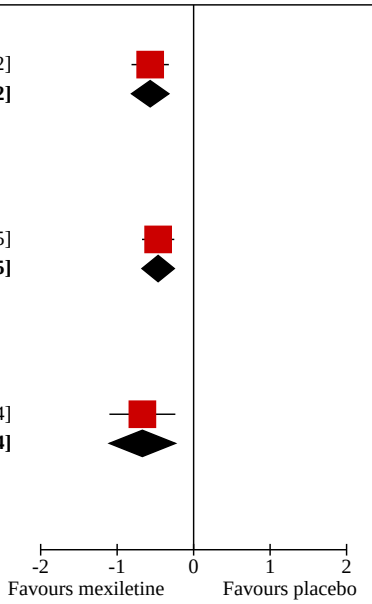
[d]Tau² calculated by DerSimonian and Laird method.

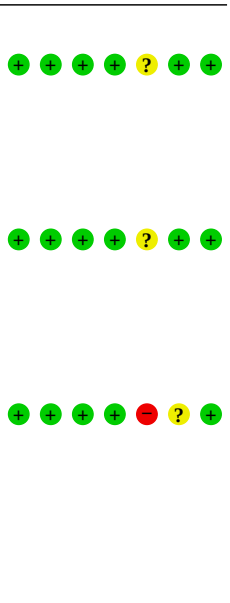
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Mexiletine versus placebo in non-dystrophic myotonias, Outcome 3: Electromyographic (EMG) relaxation time

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 Needle EMG: right abductor digiti minimi				
Statland 2012[a]	-0.568	0.1245	100.0%	-0.57 [-0.81 , -0.32]
Subtotal			**100.0%**	**-0.57 [-0.81 , -0.32]**
Test for overall effect: Z = 4.56 (P < 0.00001)				
Heterogeneity: Not applicable				
2.3.2 Needle EMG: right tibialis anterior				
Statland 2012[a]	-0.464	0.1077	100.0%	-0.46 [-0.68 , -0.25]
Subtotal			**100.0%**	**-0.46 [-0.68 , -0.25]**
Test for overall effect: Z = 4.31 (P < 0.0001)				
Heterogeneity: Not applicable				
2.3.3 Needle EMG: left rectus femoris				
Stunnenberg 2018[a]	-0.67	0.22	100.0%	-0.67 [-1.10 , -0.24]
Subtotal			**100.0%**	**-0.67 [-1.10 , -0.24]**
Test for overall effect: Z = 3.05 (P = 0.002)				
Heterogeneity: Not applicable				





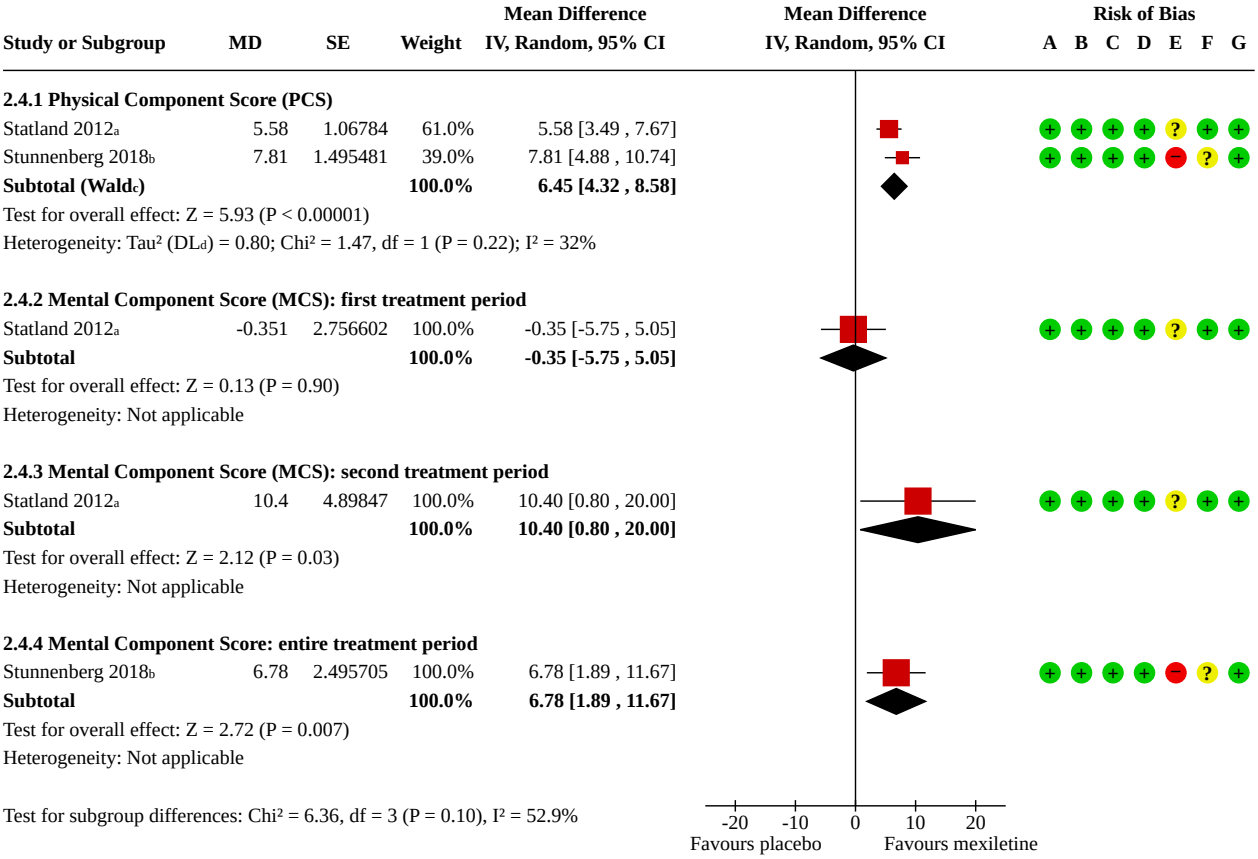
Footnotes

[a]95% CIs of MD are slightly different to those reported in Statland 2012 (derived from a linear mixed-effects model with bootstrap 95% CIs).

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Mexiletine versus placebo in non-dystrophic myotonias, Outcome 4: Quality of life: 36-item Short Form



Footnotes

[a]95% CIs of MD are slightly different to those reported in Statland 2012 (derived from a linear mixed-effects model with bootstrap 95% CIs).

[b]95% CIs of MD are slightly different to those reported in Stunnenberg 2018 (derived from a linear mixed-effects model).

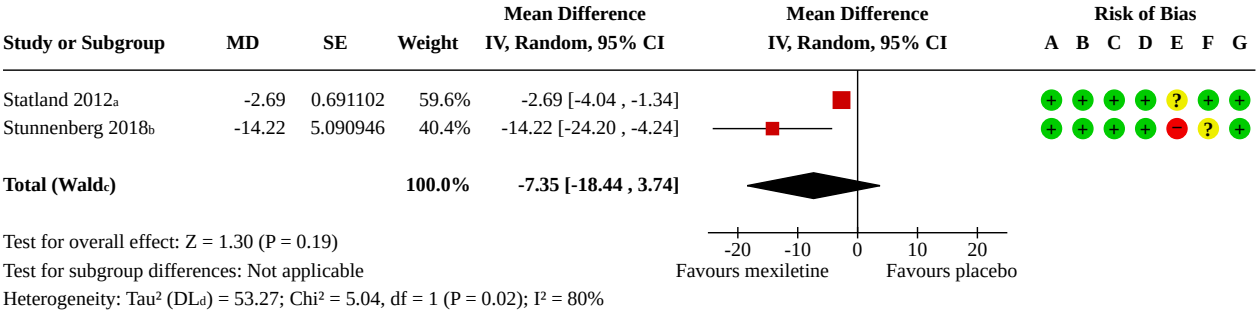
[c]CI calculated by Wald-type method.

[d]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Mexiletine versus placebo in non-dystrophic myotonias, Outcome 5: Quality of life: Individualized Neuromuscular Quality of Life



Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[d]) = 53.27; Chi² = 5.04, df = 1 (P = 0.02); I² = 80%

Footnotes

[a]95% CIs of MD are slightly different to those reported in Statland 2012 (derived from a linear mixed-effects model with bootstrap 95% CIs).
[b]95% CIs of MD are slightly different to those reported in Stunnenberg 2018 (derived from a linear mixed-effects model).
[c]CI calculated by Wald-type method.
[d]Tau² calculated by DerSimonian and Laird method.

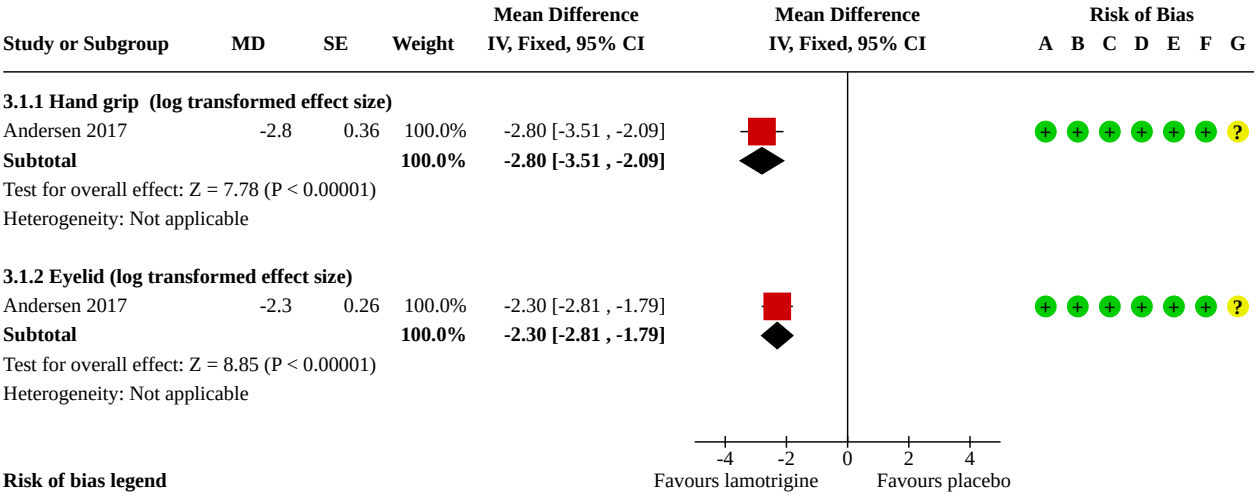
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Lamotrigine versus placebo in non-dystrophic myotonias

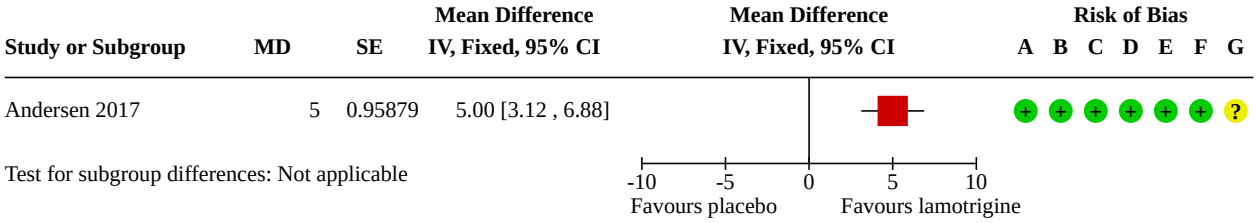
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Relaxation time (seconds, log transformed)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1.1 Hand grip (log transformed effect size)	1		Mean Difference (IV, Fixed, 95% CI)	-2.80 [-3.51, -2.09]
3.1.2 Eyelid (log transformed effect size)	1		Mean Difference (IV, Fixed, 95% CI)	-2.30 [-2.81, -1.79]
3.2 Quality of life: 36-item Short Form (overall health status)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3: Lamotrigine versus placebo in non-dystrophic myotonias, Outcome 1: Relaxation time (seconds, log transformed)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Lamotrigine versus placebo in non-dystrophic myotonias, Outcome 2: Quality of life: 36-item Short Form (overall health status)



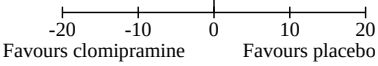
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Clomipramine versus placebo in non-dystrophic myotonias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Relaxation time	1		Mean Difference (IV, Fixed, 95% CI)	-6.69 [-12.82, -0.56]

Analysis 4.1. Comparison 4: Clomipramine versus placebo in non-dystrophic myotonias, Outcome 1: Relaxation time

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Antonini 1990	-6.69	3.1289	100.0%	-6.69 [-12.82 , -0.56]		+ ? ? ? − + +
Total			**100.0%**	**-6.69 [-12.82 , -0.56]**		



Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Summary of included studies

Study	Previous/new included	Cohort	Design	Trial medications	Number of participants	Duration of treatment periods	Washout duration	Primary outcome
Leyburn 1959	Previous	DM and NDM	Randomised, double-blind, cross-over	Quinine, procainamide 1 g, prednisolone 10 mg	15 DM, 4 NDM	3 weeks	Nil	Grip myotonia relaxation time; EMG
Lewis 1966	Previous	DM and NDM	Randomised, double-blind, cross-over	Diazepam 5 mg	19 DM, 1 NDM	3 weeks	Nil	Surface EMG relaxation time
Munsat 1967	Previous	DM and NDM	Randomised, double-blind, cross-over	Diphenylhydantoin 100 mg, procainamide 1 g	7 DM, 4 NDM	3 weeks	Nil	Ergographic grip relaxation
Finlay 1982	Previous	DM1	Randomised, double-blind, cross-over	Procainamide 500 mg vs disopyramide 200 mg	10	14 days	Nil	Hand opening time
Durelli 1983	Previous	DM1	Randomised, double-blind, cross-over	Taurine 100–150 mg	9	6 months	Nil	EMG relaxation time
Kratz 1986	Previous	DM1 and NDM	Randomised, double-blind, cross-over	Mexiletine 600 mg	4 DM, 2 NDM	Unclear	Nil	Grip strength; relaxation time.
Grant 1987	Previous	DM1	Randomised, single-blind, cross-over	Nifedipine 30 mg	10	2 weeks	Nil	Finger extension time
Gascon 1989	Previous	DM1	Randomised, double-blind, cross-over	Imipramine 375 mg	12	6 weeks	Nil	Grip myotonia relaxation time
Antonini 1990	Previous	DM1	Randomised, double-blind, cross-over	Clomipramine 75 mg	17	33 days	30 days	Grip myotonia relaxation time
Kwiecinski 1992	Previous	DM and NDM	Randomised, single-blind, cross-over/parallel	Phenytoin 600 mg, disopyramide 600 mg, mexiletine 600 mg, tocainide 1200 mg	9 DM, 21 NDM	4 weeks	Nil	Grip/eyelid myotonia relaxation time
Logigian 2010a; Logigian 2010b	New	DM1	Randomised, double-blind, cross-over	Mexiletine 150 mg/200 mg 3 times a day	46	7 weeks	4–8 weeks	Grip relaxation time

Table 1. Summary of included studies *(Continued)*

Statland 2012	New	NDM	Randomised, double-blind, cross-over	Mexiletine 200 mg	59	4 weeks	1 week	IVR
Andersen 2017	New	NDM	Randomised, double-blind, cross-over	Lamotrigine 300 mg	26	8 weeks	1–3 weeks	MBS
Bassez 2018	New	DM1	Randomised, double-blind, placebo-controlled	Metformin 3000 mg	40	52 weeks	Nil	6MWT
Stunnenberg 2018	New	NDM	Randomised, controlled (no of 1)	Mexiletine 200 mg	30	11–44 weeks	1 week	IVR
Vicart 2021	New	NDM	Randomised, double-blind, cross-over	Mexiletine 200 mg	26	18–22 days	4–8 days	VAS
Heatwole 2021	New	DM1	Randomised, double-blind, placebo-controlled	Mexiletine 150 mg	21	6 months	Nil	6MWT

6MWT: 6-Minute Walk Test; DM: myotonic dystrophy; DM1: myotonic dystrophy type 1; EMG: electromyographic; IVR: Interactive Voice Response; MBS: Myotonia Behaviour Score; NDM: non-dystrophic myotonias; VAS: Visual Analogue Scale.

Table 2. Summary of adverse events: myotonic dystrophy type 1

Study	Trial medications	Total number of participants	Number of adverse events		Number of specific adverse events reported on treatment/placebo								
			Treatment arm	Placebo arm	Gastrointestinal symptoms	Headache	Lethargy	Respiratory	Dizziness	Drowsiness	Dry mouth	Increased sweating	Other
Durelli 1983	Taurine 100–150 mg	9	0	0	—	—	—	—	—	—	—	—	—
Grant 1987	Nifedipine 30 mg	10	5	NR	—	2/NR	2/NR	—	—	—	—	—	1/NR
Gascon 1989	Imipramine 375 mg	12	48	21	—	1/3	—	—	4/1	4/3	8/2	4/2	27/10
Antonini 1990	Clomipramine 75 mg	17	12	2	—	—	2/2	—	1/0	6/0	2/0	1/0	—

Table 2. Summary of adverse events: myotonic dystrophy type 1 *(Continued)*

Logigian 2010a	Mexiletine 150 mg	18	17	10	6/4	2/1	—	4/2	1/0	—	—	—	4/3
Logigian 2010b	Mexiletine 200 mg 3 times a day	18	24	13	6/0	5/6	—	4/5	3/0	—	—	—	6/2
Bassez 2018[a]	Metformin 3000 mg	40	4	1	1/0	—	—	1/0	—	—	—	—	2/1
Heatwole 2021	Mexiletine 150 mg	21	41	32	15/10	3/3	12/15	—	4/1	—	—	—	7/3

NR: not reported.
[a]Serious adverse events only reported.

Table 3. Summary of adverse events: non-dystrophic myotonias

Study	Trial medications	Total number of participants	Number of adverse events		Number of specific adverse events reported on treatment/placebo							
			Treatment arm	Placebo arm	Gastrointestinal symptoms	Headache	Lethargy/constitutional	ECG changes/ palpitations	Dizziness	Rash	Insomnia	Other
Kwiecinski 1992[a]	Mexiletine 600 mg[b]	30	2	0	2/0	—	—	—	—	—	—	—
Statland 2012	Mexiletine 200 mg	59	24	11	9/1	—	3/0	1/1	—	1/2	—	10/9
Andersen 2017	Lamotrigine 300 mg	26	44	23	2/3	11/6	6/5	2/1	6/2	3/1	—	12/5
Stunnenberg 2018	Mexiletine 200 mg	30	28	4	21/1	1/1	—	2/0	—	1/0	1/0	2/0
Vicart 2021	Mexiletine 200 mg	26	40	14	4/NR	—	—	1/NR	—	—	3/NR	—

ECG: electrocardiogram; NR: not reported.
[a]9 participants with myotonic dystrophy and 21 participants with non-dystrophic myotonias. Adverse events not reported separately.
[b]Only descriptive information presented for other treatments.

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRSW) search strategy

1 MeSH DESCRIPTOR Myotonia WITH DT AND INREGISTER 0

2 MeSH DESCRIPTOR Myotonic Disorders WITH DT AND INREGISTER 0

3 MeSH DESCRIPTOR Paralysis, Hyperkalemic Periodic WITH DT AND INREGISTER 0

4 #1 or #2 or #3 0

5 myotonia* AND INREGISTER 24

6 myotonic NEAR3 dystroph* AND INREGISTER 59

7 "myotonic disorder*" AND INREGISTER 3

8 "myotonia congenita" AND INREGISTER 5

9 "thomsen* disease*" AND INREGISTER 0

10 "becker* disease*" AND INREGISTER 0

11 "hyperkalemic periodic paralysis" AND INREGISTER 2

12 #5 or #6 or #7 or #8 or #9 or #10 or #11 73

13 treatment or therapy AND INREGISTER 6555

14 #12 and #13 61

15 #4 or #14 61

16 INCENTRAL AND INREGISTER 7221

17 #15 NOT #16 1

Appendix 2. CENTRAL (CRSW) search strategy

1 MeSH DESCRIPTOR Myotonia WITH DT AND CENTRAL:TARGET 13

2 MeSH DESCRIPTOR Myotonic Disorders WITH DT AND CENTRAL:TARGET 4

3 MeSH DESCRIPTOR Paralysis, Hyperkalemic Periodic WITH DT AND CENTRAL:TARGET 0

4 #1 or #2 or #3 15

5 myotonia* AND CENTRAL:TARGET 100

6 myotonic NEAR3 dystroph* AND CENTRAL:TARGET 160

7 "myotonic disorder*" AND CENTRAL:TARGET 17

8 "myotonia congenita" AND CENTRAL:TARGET 19

9 "thomsen* disease*" AND CENTRAL:TARGET 6

10 "becker* disease*" AND CENTRAL:TARGET 1

11 "hyperkalemic periodic paralysis" AND CENTRAL:TARGET 8

12 #5 or #6 or #7 or #8 or #9 or #10 or #11 227

13 treatment or therapy AND CENTRAL:TARGET 1195108

14 #12 and #13 162

15 INREGISTER 7877

16 #14 NOT #15 102

17 26/01/2022_TO_29/03/2023:CRSINCENTRAL AND CENTRAL:TARGET 166235

18 #17 AND #16 11

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to March 28, 2023>

1 randomized controlled trial.pt. (589740)

2 controlled clinical trial.pt. (95229)

3 randomized.ab. (597895)

4 placebo.ab. (236977)

5 drug therapy.fs. (2577150)

6 randomly.ab. (405069)

7 trial.ab. (641803)

8 groups.ab. (2496159)

9 or/1-8 (5617869)

10 exp animals/ not humans.sh. (5107161)

11 9 not 10 (4900170)

12 Myotonia/dt (137)

13 exp Myotonic Disorders/dt (313)

14 Paralysis, Hyperkalemic Periodic/dt (13)

15 or/12-14 (444)

16 myotonia$.mp. (3755)

17 (myotonic adj3 dystroph$).tw. (6008)

18 myotonic disorder$.tw. (108)

19 myotonia congenita.tw. (505)

20 thomsen$ disease$.tw. (119)

21 becker$ disease$.tw. (51)

22 hyperkalemic periodic paralysis.tw. (273)

23 or/16-22 (9129)

24 (treatment or therapy).mp. (8892009)

25 (11 and 15) or (11 and 23 and 24) (732)

26 remove duplicates from 25 (729)

27 limit 26 to ed=20220126-20230329 (34)

28 limit 26 to dt=20220126-20230329 (25)

29 27 or 28 (35)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2023 Week 12>

1 crossover-procedure/ (74609)

2 double-blind procedure/ (208615)

3 randomized controlled trial/ (775960)

4 single-blind procedure/ (51177)

5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (2765147)

6 or/1-5 (2875302)

7 human/ (25105782)

8 6 and 7 (2271588)

9 nonhuman/ or human/ (30373478)

10 6 not 9 (361634)

11 8 or 10 (2633222)

12 limit 11 to (conference abstracts or embase) (2074669)

13 MYOTONIA/dt (277)

14 myotonic dystrophy/dt (322)

15 Thomsen disease/dt (125)

16 BECKER MUSCULAR DYSTROPHY/dt (213)

17 periodic paralysis/dt (252)

18 or/13-17 (1070)

19 myotonia$.mp. (4447)

20 (myotonic adj3 dystrophy).mp. (10546)

21 myotonic disorder$.mp. (178)

22 thomsen$ disease$.mp. (1224)

23 Becker Muscular Dystrophy.mp. (4062)

24 becker$ disease$.mp. (77)

25 paramyotonia$ congenita$.mp. (398)

26 hyperkalemic periodic paralysis.mp. (334)

27 or/19-26 (17410)

28 (treatment or therapy).mp. (12967481)

29 (12 and 18) or (12 and 27 and 28) (292)

30 remove duplicates from 29 (285)

31 limit 30 to em=202203-202312 (5)

Appendix 5. ClinicalTrials.gov search strategy

Advanced Search

Condition or disease:Myotonia OR Myotonic OR "Hyperkalemic Periodic Paralysis"

Study type:Interventional Studies (Clinical Trials)

First posted on or after 01/26/2022

7 Studies Found

Appendix 6. World Health Organization Internation Clinical Trials Registry Platform search strategy

Advanced Search

Myotonia OR Myotonic OR Hyperkalemic Periodic Paralysis ***in the Condition***

Recruitment status is ALL

Date of registration is between 01/01/2022 ***and*** 29/03/2023

8 records for 8 trials found

WHAT'S NEW

Date	Event	Description
8 April 2025	New search has been performed	New search conducted March 2023 and additional data analysis
8 April 2025	New citation required and conclusions have changed	Baziel GM van Engelen withdrew at this update and three new review authors joined; two experts in the field of neuromuscular disorders (Vinojini Vivekanandam, Jennifer Spillane) and a statistician (Sarah Nevitt). Seven new studies were included at this update with 249 participants (106 with myotonic dystrophy and 143 with non-dystrophic myotonia), bringing the total to 17 included studies involving 392 participants (219 with myotonic dystrophy type 1 and 173 with non-dystropic myotonia). Methods were updated for the analysis of cross-over studies. Moderate-certainty evidence suggests that mexiletine and lamotrigine are probably efficacious and well-tolerated treatments for non-dystrophic myotonias.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 1, 2006

Date	Event	Description
9 April 2012	New search has been performed	Searches updated to September 2010. Two new RCTs were found. Conclusions changed for myotonic dystrophy type I. Baziel GM van Engelen withdrew from authorship at this update.
29 April 2008	Amended	Converted to new review format.
25 February 2008	New search has been performed	Searches updated to 31 December 2007. One additional study, Alfonsi 2007 added to excluded studies.

Date	Event	Description
5 October 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JS, VV, GT, GD, and CF performed data curation/retrieval.

SN performed statistical analysis.

JS wrote a first draft.

VV wrote the final version and performed some analyses.

All others reviewed and edited the final version.

VV and SN performed all manuscript revisions.

DECLARATIONS OF INTEREST

VV: declared involvement in an eligible study, as chief investigator of MEND (MExiletine versus lamotrigine in Non-Dystrophic myotonia) (NCT05017155), grant and charity funded. VV was not involved in eligibility decisions, data extraction, risk of bias, or GRADE assessments for this study.

JS: UCB UK (Travel), argenx (Independent Contractor – Consultant), UCB UK (Independent Contractor – Consultant), argenx (Travel).

JT: none.

GD: none.

CGF: Maastricht Universitair Medisch Centrum (Employment), OliPass (Independent Contractor – Consultant), Sangamo (Independent Contractor – Consultant).

MGH: declared involvement in eligible studies, Statland 2012 and NCT05017155, funded by Neuromuscular Study Group, Jon Moulton Charity Trust, UCLH BRC Fast Track Grant. MGH was not involved in eligibility decisions, data extraction, risk of bias, or GRADE assessments for these studies.

SN: Statistical Editor of the Cochrane Neuromuscular Group up to March 2023. SN was not involved in the editorial process of this review.

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- No sources of support provided

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  (MAR04-0118)
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- Queen Square Centre for Neuromuscular Diseases, UK

  Support for Cochrane Neuromuscular

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Baziel GM van Engelen withdrew at this update. New review authors: Vinojini Vivekanandam, Jennifer Spillane, and Sarah Nevitt. Authors are experts in the field of neuromuscular disorders. SN is a statistician.

We clarified the inclusion and exclusion criteria for the types of participants eligible for this review in this update.

We clearly defined the primary outcome and secondary outcomes for this update in order to define included studies in a highly heterogeneous rare disease. As such, we included randomised controlled trials and that a validated participant-reported outcome must be used. The remit of this Cochrane review was particularly to define treatment scope for myotonia, not myopathy or mobility. This was agreed by all authors. Secondary outcome measures included other measures of myotonia, including electromyographic measures, timed measures, and quality of life measures as detailed in the Methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Calcium Channel Blockers [therapeutic use]; *Myotonia [drug therapy]; Myotonic Dystrophy [drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans