Mexiletine versus lamotrigine in non-dystrophic myotonias: a randomised, double-blind, head-to-head, crossover, non-inferiority, phase 3 trial

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See Comment page 953

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Summary

Background Non-dystrophic myotonias are skeletal muscle channelopathies caused by ion channel dysfunction. Symptom onset is frequently in the first decade of life, causing disability in a young cohort. Although there is no cure, symptomatic treatments exist. Previous trials provide evidence of the efficacy of mexiletine. More recently, lamotrigine has been shown to be effective. Both treatments have different profiles, including pharmacokinetics and adverse events. This trial aimed to investigate whether lamotrigine is non-inferior to mexiletine to directly inform clinical practice.

Methods We did a randomised, double-blind, crossover, non-inferiority, phase 3 trial at the National Hospital for Neurology and Neurosurgery (London, UK). Participants (aged ≥18 years) who had genetically confirmed symptomatic non-dystrophic myotonia were randomly assigned (1:1), by means of a block randomisation schedule created by a computer program, to receive either mexiletine for 8 weeks followed by lamotrigine for 8 weeks, or lamotrigine followed by mexiletine, with a 7-day washout period in between. Investigators and participants were masked to treatment allocation. The primary outcome measure was the mean interactive voice response (IVR) diary stiffness score (0–9 scale) over the participant's final 2 weeks of diary reporting in each treatment period. Non-inferiority was assessed using a mixed-effects model with a predefined margin of 0·5 and included all randomly assigned participants who contributed at least 7 days of IVR-diary data in either treatment period. The trial is registered at ClinicalTrials.gov, NCT05017155, and EudraCT, 2020-003375-17.

Findings Between Aug 1, 2021, and Dec 12, 2022, of 60 participants were screened (24 females and 36 males) and randomly assigned between Aug 1, 2021 and Dec 12, 2022, to either the mexiletine–lamotrigine sequence (n=30) or the lamotrigine–mexiletine sequence (n=30). 53 participants contributed data to the primary analysis. The mean IVR stiffness score after treatment with mexiletine was 2·54 (95% CI 1·98 to 3·10) versus 2·77 (2·21 to 3·32) with lamotrigine (mean mexiletine–lamotrigine difference –0·23 [95% CI –0·63 to 0·17]). The most common adverse event with both treatments was indigestion–reflux (eight participants, 208 participant-days receiving mexiletine; seven participants, 130 participant-days receiving lamotrigine). No serious adverse events were reported.

Interpretation We were unable to conclude that lamotrigine is non-inferior to mexiletine; however, improvements in all outcome measures from baseline were similar between lamotrigine and mexiletine. Lamotrigine is an important treatment consideration in non-dystrophic myotonias alongside mexiletine; we propose a treatment algorithm to guide clinical practice.

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Introduction

Non-dystrophic myotonias are a group of rare genetic neuromuscular disorders with symptom onset predominantly within the first two decades of life, causing lifelong morbidity. The hallmark of these disorders is that symptoms occur in an episodic or paroxysmal fashion, causing impairment of mobility and acute disability. The non-dystrophic myotonias include myotonia congenita, paramyotonia congenita, and sodium channel myotonia. They have a point prevalence in England of 1·12 per 100 000 people.[1] Myotonia congenita is caused by mutations in the *CLCN1* gene, which codes for the muscle chloride channel ClC-1.[2] Sodium channel myotonia and paramyotonia congenita are caused by mutations in the *SCN4A* gene, which codes for the skeletal muscle voltage-gated sodium channel Nav1.4.[3] Both of these channels are essential for regulating normal muscle membrane excitability, muscle contraction, and relaxation. Non-dystrophic myotonias are therefore unified by a common pathomechanism of altered muscle membrane excitability.[4] The membrane becomes hyperexcitable, resulting in spontaneous depolarisation and contraction after a motor nerve stimulus.[2]

Research in context

Evidence before this study

We searched PubMed on Sept 5, 2023 for clinical trials in non-dystrophic myotonias, using the search terms "myotonia", "treatment", and "efficacy", without language restrictions. Trials including patients with myotonic dystrophy were excluded. We found several small trials, which are subject to bias and provide only low-level evidence, for medications including phenytoin, quinine, tricyclic antidepressants, and procainamide. Robust, moderate–high evidence from randomised, double-blind, placebo-controlled trials was found only for mexiletine and lamotrigine. Mexiletine has been shown to improve stiffness scores on a validated patient-reported outcome measure compared with placebo; however, adverse events including gastrointestinal issues were commonly reported. Lamotrigine has also been reported to be effective in reducing a validated patient-reported outcome measure of myotonia compared with placebo. However, no randomised, double-blind, head-to-head trials have been done.

Added value of this study

Mexiletine is a first-line treatment for non-dystrophic myotonias. However, a significant proportion of patients (up to one-third) treated with mexiletine develop side-effects; it cannot be prescribed in pregnancy, when myotonia often worsens; it has been shown to be less beneficial for patients with myotonia congenita than for those with sodium channel myotonia or paramyotonia congenita; and in some countries it is expensive and access is restricted. Owing to its anti-arrhythmic potential, mexiletine is also contraindicated in patients with cardiac conditions. With the recently established efficacy of lamotrigine and potential advantages in terms of safety and cost, there is equipoise as to the first-line treatment. This study aimed to establish whether lamotrigine is non-inferior to mexiletine to guide clinical practice. Our findings have enabled us to suggest a personalised treatment algorithm for patients with non-dystrophic myotonias.

Implications of all the available evidence

Head-to-head studies in clinical practice are crucial to inform clinical care and prescribing choice. This head-to-head comparison of mexiletine and lamotrigine has provided additional high-quality data, which are needed to inform symptomatic treatment of non-dystrophic myotonias.

The primary clinical manifestation of non-dystrophic myotonia is myotonia—ie, delayed relaxation of skeletal muscle after contraction. Myotonia is experienced by patients as muscles locking, stiffness, or cramping. Symptoms commonly affect the leg muscles and are precipitated by sudden or initial movement leading to falls and injury. They are also exacerbated by prolonged sitting, especially after physical activity, and changes in environmental temperature. These difficulties limit independence, social activity, and choice of employment, and are often socially embarrassing. The symptomatic relationship with activity often leads to sedentary behaviour, which in turn is a risk factor for additional comorbidities (eg, heart disease or stroke).[5] The condition is frequently painful, with pain and impaired physical ability affecting quality of life considerably.[6] Symptoms commonly worsen during pregnancy, which can be compounded by the need to discontinue current pharmacological therapies owing to a lack of safety information on their use during pregnancy.[7]

There is no cure or disease-modifying treatment for non-dystrophic myotonias, but sodium channel blockers are used for symptomatic relief. An international, multicentre, randomised, placebo-controlled study (n=59) has shown that the sodium channel blocker mexiletine is effective in reducing myotonia and improving quality of life.[8] Trials of mexiletine before this large, rigorous trial appear to have included only patients with myotonic dystrophy and had small sample sizes. More recent studies (n=30 in an aggregated n-of-1 trial; n=25 in a randomised crossover trial) have added supportive evidence of the efficacy of mexiletine.[9,10] Mexiletine has become the first-line treatment for non-dystrophic myotonias, but not all patients respond to the drug and up to one-third develop side-effects, the most common being gastrointestinal disturbances.[11] Additionally, from origins as an anti-arrhythmic medication, it is contraindicated in patients with cardiac conditions. Screening with annual electrocardiograms is required for patients taking mexiletine and, in some countries, additional cardiac surveillance is also mandated. Mexiletine has also been shown to be less beneficial for patients with myotonia congenita than for those with sodium channel myotonia or paramyotonia congenita.[11] Mexiletine cannot be prescribed during pregnancy, when myotonia often worsens. In the UK, mexiletine is expensive and access is restricted. Little evidence exists for use of other medications. Small trials, subject to bias and providing low levels of evidence, have been done for medications including phenytoin, taurine–quinine, tricyclic antidepressants, and procainamide, but have not provided data to support the clinical use of these drugs.[12–15] Small trials have shown efficacy for other sodium channel blockers, including flecainide and ranolazine; however, larger, randomised controlled trials are needed.[16] In 2021, lamotrigine was shown to be effective in a dose-dependent manner in non-dystrophic myotonias.[17] The trial was stopped early owing to efficacy, although this decision resulted in a small sample size of n=26. Lamotrigine was well tolerated in the trial participants.

With clinical equipoise established, a head-to-head trial is needed for comparison of mexiletine and lamotrigine to inform clinical practice. Given the potential advantages of lamotrigine in terms of the adverse event profile and

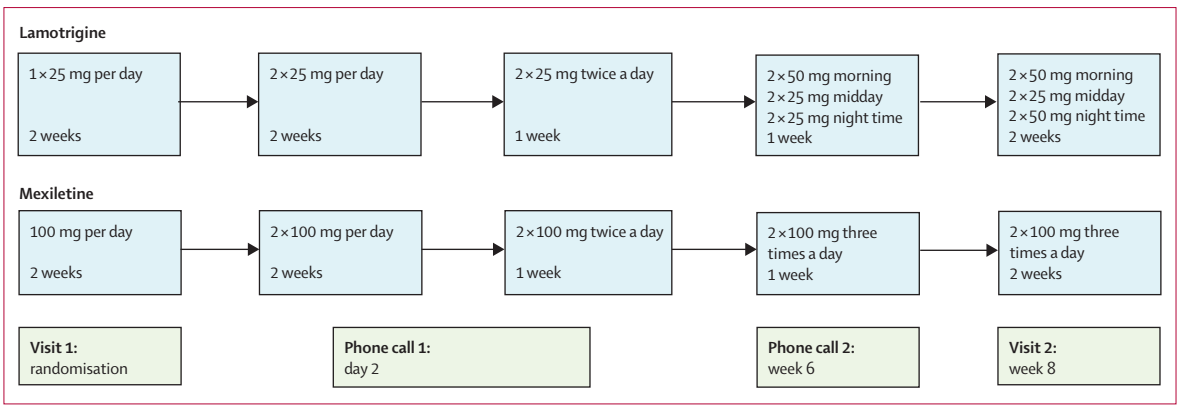

Figure 1: **Medication up-titration regimens**
After screening, visits occurred at randomisation, week 8 of period 1, and week 8 of period 2. Additional phone calls were made at day 2 and week 6 of each period.

(especially) cost, we aimed to establish whether lamotrigine is non-inferior to mexiletine.

Methods

Study design and participants

We did a randomised, double-blind, head-to-head, cross-over, non-inferiority, phase 3 trial at the National Hospital for Neurology and Neurosurgery (NHNN); Queen Square, London, UK), which runs the NHS UK commissioned Highly Specialised Service for Skeletal Muscle Channelopathies, receiving referrals for patients with non-dystrophic myotonias from across the UK. Adult participants (aged ≥18 years) were enrolled from NHNN with genetically confirmed non-dystrophic myotonia, symptomatic myotonia (Myotonia Behaviour Score[18] ≥1), and the ability to safely discontinue all other antimyotonia treatment for the duration of the study. The main exclusion criteria were: pregnancy and breastfeeding; concurrent or recent exposure to medication that would interact with the study medication; allergy to the investigational medicinal products (IMP); concomitant medication that would affect the IMP (eg, valproate); severe renal impairment; severe hepatic impairment; and severe cardiac disease (including ischaemic heart disease, heart failure, and rhythm disturbance).

Written informed consent was obtained from all participants. The study was approved by the University College London and University College London Hospital Joint Research Organisation as well as the NHS HRA Research Ethics Committee (REC 21/EM/0018) and is registered on clinicaltrials.gov, NCT05017155, and EudraCT, 2020-003375-17.

Randomisation and masking

After consent and washout of any other antimyotonic medication, participants were randomly assigned (1:1) by means of block randomisation (block size 4) to one of two treatment sequences: lamotrigine followed by mexiletine or mexiletine followed by lamotrigine, stratified by genetic variant (*SCN4A* or *CLCN1*). The randomisation schedule was created online by Sealed Envelope (Sealed Envelope 2024, London, UK) and sent directly to the study site pharmacist.[19] Investigators and participants were masked to treatment allocation and block size. Masking was achieved by over-encapsulation of study medication. Only the study site pharmacists who prepared the treatment schedules and bottles had access to treatment allocations for individual participants.

Procedures

The first treatment period consisted of 8 weeks. This was followed by a 7-day drug washout period and a second 8-week treatment period. The total duration of the trial per participant was up to 18 weeks (16 weeks of treatment plus 5 days to 2 weeks for drug washout). When receiving the oral lamotrigine treatment, the participant commenced at a dose of 25 mg daily for 2 weeks, increased to 25 mg twice daily for 2 weeks, increased to 50 mg twice daily for 1 week, increased to 100 mg in the morning, 50 mg at midday, and 50 mg at night for 1 week, then increased to 100 mg in the morning, 50 mg at midday, and 100 mg at night for the final 2 weeks. When receiving oral mexiletine treatment, the participant commenced at a dose of 100 mg daily for 2 weeks, increased to 200 mg daily for 2 weeks, increased to 200 mg twice daily for 1 week, increased to 200 mg three times a day for 1 week, then remained on 200 mg three times a day for the final 2 weeks (figure 1). Participants remained masked to treatment as the number of capsules and dosing frequencies were matched regardless of the medication group to which they were allocated.

After screening, visits occurred at randomisation, week 8 of period 1, and week 8 of period 2. Additional phone calls were done at day 2 and week 6 of each period. Conversion from in-person visits to phone or video calls was permitted and predefined in the protocol, if travel was precluded as a result of COVID-19 restrictions. The schedule of all trial assessments and procedures is delineated in the appendix (p 1); both phone assessments

See Online for appendix

and visits occurred within 5 days of the scheduled date. Adverse events were assessed at each telephone consultation and in-person visit. Patients who withdrew from the trial had an end-of-trial visit, with the reason for withdrawal recorded. Participants who completed the trial were additionally asked to guess the identity of their assigned treatment sequence.

Outcomes

The primary outcome variable was a stiffness score ascertained by an interactive voice response (IVR) diary, adapted from the IVR to a paper-based version, averaged over the last 2 weeks of each treatment period during which the participant contributed diary data. This is a validated and clinically relevant outcome previously used in a large international, multicentre clinical trial of mexiletine.[20] The score was ascertained daily and recorded on a paper diary with weekly email or call reminders. Stiffness was measured on a 0–9 scale, with 0 being no stiffness, 1 being minimal stiffness, and 9 being the worst stiffness ever experienced.

Secondary outcome variables included the validated myotonia behaviour score (MBS).[18] The MBS was recorded daily on a 0 to 5 scale in regard to stiffness. The average MBS over the last 2 weeks of each treatment period was used for analysis. All other secondary outcome variables were recorded at randomisation and at the end of each period. The brief pain inventory yields four pain severity scores for worst, least, average, and current pain, as well as a pain interference score that is the average over seven interference items, each scored on a 0 to 10 scale.[21] The modified fatigue severity scale consists of nine questions in regard to fatigue, each rated on a 1 to 7 scale, yielding a total score ranging from 1 to 63. The Medical Outcomes Study Short Form-36 Questionnaire (SF-36) version 1.0 is a 36-item questionnaire to assess overall health status, yielding eight subscale scores ranging from 0 to 100, with higher scores indicating better health status.[22] The timed-stands test (TST) required participants to stand up (to upright) and sit down ten times from an armless chair of 45 cm height, as quickly as possible. The time taken to do this was recorded with a stopwatch. For the timed up and go (TUG), the participant was asked to rise from an armchair of 45 cm height, walk 3 m, turn around, walk back and sit down again at a self-selected speed. The time taken to do this was recorded with a stopwatch. This was done three times and the average recorded. A post-hoc analysis included participants who had fully completed diary data in both treatment periods.

The trial was done during periods of COVID-19 restrictions and waves in the UK. The protocol was written and approved with all precautions in place. However, owing to difficulties in doing the TUG test during the COVID-19 pandemic (difficulties ranged from isolation requirements to lack of access to measuring equipment in virtual visits), this assessment was not consistently done and TUG was dropped as an outcome measure.

Adverse events were recorded at each phone call and visit. An adverse event was defined as any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the study medication. The severity, duration, and required treatment was recorded. Compliance with treatment was assessed by use of a diary and pill counts of returned study medication.

Statistical analysis

The trial was designed to establish whether lamotrigine is non-inferior to mexiletine with respect to mean stiffness severity over a 2-week period, as measured by the IVR-diary stiffness score. Lamotrigine would be judged to be non-inferior to mexiletine if the 95% CI for the mean mexiletine–lamotrigine difference in stiffness severity excluded treatment differences exceeding 0·50 units in favour of mexiletine. This non-inferiority margin was chosen on the basis of the estimated effect (*vs* placebo) of 1·68 points in the mexiletine trial by Statland

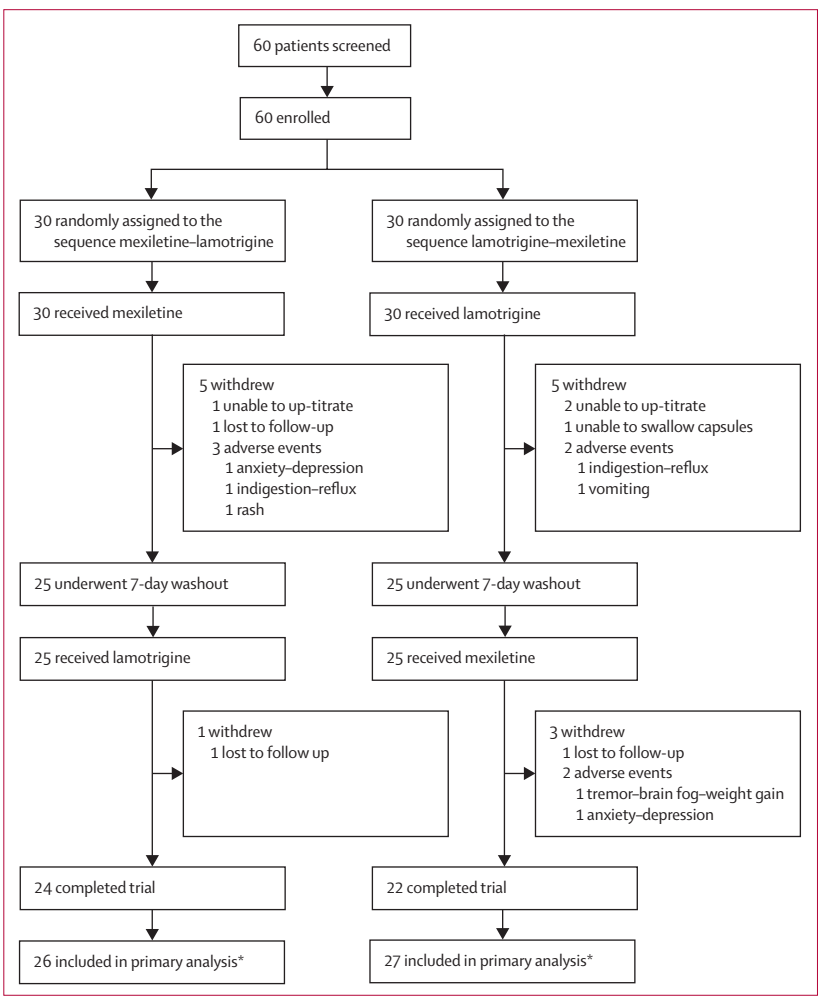

Figure 2: **Trial profile**
*Adequate diary data for the primary outcome variable were available for 26 participants in the mexiletine–lamotrigine sequence and 27 in the lamotrigine–mexiletine sequence.

and colleagues[8] and the fact that a difference in mean response between mexiletine and lamotrigine of at least 0·50 points would indicate that lamotrigine preserves at least 70% of the effect (*vs* placebo) of mexiletine.

Assuming an SD of 1·25 points for the primary outcome variable,[8] and that mexiletine and lamotrigine have the same effects, a sample size of 52 participants would provide 80% power to detect non-inferiority of lamotrigine, by use of a *t* test with a one-tailed significance level of 2·5%. The sample size was inflated to 60 participants to account for an anticipated 10–15% participant withdrawal.

	Mexiletine–lamotrigine (n=30)	Lamotrigine–mexiletine (n=30)
Age, years	44·0 (16·0)	39·2 (13·0)
Age at symptom onset, years	8·6 (5·4)	6·7 (5·4)
Creatine kinase, U/L	333·5 (234·4)	373·6 (291·3)
Diagnosis		
Myotonia congenita	19 (63%)	16 (53%)
Paramyotonia congenita	8 (27%)	9 (30%)
Sodium channel myotonia	3 (10%)	5 (17%)
Sex		
Female	11 (37%)	13 (43%)
Male	19 (63%)	17 (57%)
Race		
White	26 (87%)	25 (83%)
Black	0	1 (3%)
Asian	2 (7%)	3 (10%)
Other	2 (7%)	1 (3%)
Activity level*		
Sedentary	5 (17%)	6 (20%)
Moderate activity	16 (53%)	19 (63%)
Significant activity	9 (30%)	9 (30%)
Family history	20 (67%)	19 (63%)
Pre-trial medication		
Mexiletine	16 (53%)	14 (47%)
Lamotrigine	1 (3%)	1 (3%)
Acetazolamide	1 (3%)	1 (3%)
None	12 (40%)	14 (47%)
Interactive voice response-diary stiffness score	4·90 (2·60)	5·71 (2·31)
Myotonia Behaviour Score	2·79 (1·03)	3·07 (0·90)
Brief Pain Inventory Average Pain	2·85 (2·98)	3·90 (2·70)
Fatigue Severity Scale	37·1 (16·3)	37·7 (12·6)
Timed stands test, s	36·2 (18·5)	38·3 (22·1)
Medical Outcomes Study Short Form-36 Questionnaire subscale		
Physical functioning	57·9 (26·3)	49·8 (31·5)
Role-physical	47·3 (46·3)	35·3 (37·5)
Bodily pain	60·1 (32·0)	46·7 (24·9)
Social functioning	63·4 (32·4)	52·6 (25·7)
Mental health	64·3 (22·6)	59·0 (22·4)
Role-emotional	59·5 (43·9)	37·9 (41·5)
Vitality	41·1 (24·5)	37·1 (20·3)
General health	51·6 (27·7)	49·7 (20·6)

Data are mean (SD) or n (%). *Patient-reported via diary: sedentary=minimal activity daily; moderate activity=daily activity, walking, or household tasks; significant activity=exercise >30 min.

Table 1: **Baseline characteristics of trial participants**

The primary analysis of the primary outcome variable of stiffness severity included all randomly assigned participants who contributed at least 7 days of IVR-diary data in either treatment period. The primary outcome variable was computed as the average stiffness score over the final 2 weeks during which the participant contributed IVR-diary data; for participants contributing between 7 and 13 days of IVR-diary data, the average stiffness score over those days was used. If fewer than 7 days of IVR-diary data were available, the outcome was set to missing for that treatment period.

The primary outcome measure was analysed by use of a mixed-effects analysis of variance model with fixed effects for treatment and period and a random effect for participant.[23] A 95% CI was calculated for the mean of the mexiletine–lamotrigine differences (treatment effect) by use of this model. The Kenward–Roger method was used to establish the denominator degrees of freedom for inference. The mixed-effects models incorporate all available data from participants and accommodate missing data in an appropriate way under the missing-at-random assumption.[24]

Secondary outcome variables that are approximately normally distributed were analysed by use of the methods described for the primary outcome variable. Model assumptions (normality, homoscedasticity, absence of treatment-by-period interaction) were examined by use of numerical and graphic techniques.[25] The analyses included all randomly assigned participants who contributed outcome data in either treatment period.

Adverse events and treatment compliance were summarised by treatment condition. Guessed treatment sequence from the blindedness questionnaire was tabulated by actual treatment sequence. Fisher's exact test was used to establish whether the proportion of participants who guessed that they first received mexiletine treatment differed among the actual treatment sequences. A masked data and safety monitoring committee met twice over the course of the trial to review any adverse events.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 1, 2021 and Dec 12, 2022, of 60 participants screened, 60 were enrolled (figure 2). The final participant had their final study visit on April 9, 2023. 14 study participants withdrew from the trial. Three were lost to follow-up (two receiving mexiletine and one receiving lamotrigine). One participant receiving lamotrigine was unable to swallow the capsules owing to throat or

laryngeal myotonia and withdrew. Three participants (one receiving mexiletine and two receiving lamotrigine) withdrew owing to notable myotonia while receiving the lower treatment dose in the first 2–3 weeks on the up-titration schedule. They withdrew from the study to return to their pretrial myotonic treatment. Seven participants withdrew owing to adverse events. One participant who was receiving lamotrigine had vomiting, which continued after treatment was stopped and was thought to be unrelated to treatment. Another participant developed a rash while receiving mexietine and withdrew from the trial, but after seeking medical review for the rash, this was also thought to be unrelated. Of the five remaining participants, four withdrawals were owing to adverse events from mexiletine (figure 2). One participant who was receiving lamotrigine withdrew owing to indigestion or reflux. All participants' adverse events improved after stopping the trial.

Baseline characteristics were similar between the treatment allocation groups (table 1). The mean age of the cohort was 41·6 years (SD 14·6), and the mean age at symptom onset was 7·7 years (5·5). Mean creatinine kinase concentration was 353·53 IU/L (SD 262·87). Mean vital signs were a heart rate of 73·6 beats per min (SD 44·6), a corrected QT interval of 411·3 (24·5), and a PR interval of 157·7 (44·6). Mean IVR-stiffness score was 5·30 (SD 2·47) and the mean MBS was 2·93 (SD 0·97). The TUG test could not to be done owing to COVID-19 restrictions.

Adequate diary data for the primary outcome variable were available for 26 participants (87%; 24 in both periods, two in period 1 only) in the mexiletine–lamotrigine sequence and 27 participants (90%; 23 in both periods, four in period 1 only) in the lamotrigine–mexiletine sequence. Table 2 provides the mean values at baseline, during mexiletine treatment, and during lamotrigine treatment, as well as the mexiletine–lamotrigine treatment difference, for the primary and secondary outcome variables. The mean treatment difference in stiffness severity for the primary outcome measure (IVR-diary stiffness score) was –0·23 (95% CI –0·63 to 0·17). Hence, non-inferiority of lamotrigine to mexiletine was not shown, with the CI containing values indicating a treatment difference of more than 0·50 in favour of mexiletine. A post-hoc sensitivity analysis that included only 42 participants who had fully completed diary data in both treatment periods yielded very similar results (mean treatment difference –0·22, 95% CI –0·58 to 0·14). The mean IVR-stiffness scores do suggest efficacy of both mexiletine and lamotrigine, with scores during treatment being reduced by approximately 50% from baseline. Similar results were observed for the MBS, pain scores, fatigue, timed-stands test, and SF-36 subscale scores. No evidence of a treatment-by-period interaction was apparent.

The percentage reductions from baseline of the scores on selected outcomes after treatment with either mexiletine or lamotrigine are shown in the appendix (p 2). The percentage reductions are similar for mexiletine and lamotrigine treatment across all outcomes.

	Total cohort baseline mean	Mexiletine mean after treatment (95% CI)*	Lamotrigine mean after treatment (95% CI)*	Treatment difference (95% CI)*
Primary outcome				
Interactive voice response-diary stiffness score	5·30	2·54 (1·98 to 3·10)	2·77 (2·21 to 3·32)	–0·23 (–0·63 to 0·17)
Secondary outcomes				
Myotonia Behaviour Score	2·93	1·67 (1·33 to 2·01)	1·76 (1·43 to 2·09)	–0·09 (–0·38 to 0·20)
Brief Pain Inventory				
Worst pain	4·25	2·43 (1·60 to 3·26)	2·69 (1·88 to 3·50)	–0·26 (–1·00 to 0·48)
Least pain	1·91	1·03 (0·46 to 1·61)	1·33 (0·76 to 1·89)	–0·30 (–0·72 to 0·12)
Average pain	3·39	2·10 (1·38 to 2·82)	2·09 (1·38 to 2·80)	0·01 (–0·48 to 0·50)
Current pain	2·82	1·63 (0·98 to 2·29)	1·62 (0·97 to 2·26)	0·01 (–0·39 to 0·42)
Pain interference	3·34	1·99 (1·22 to 2·76)	2·26 (1·50 to 3·02)	–0·27 (–0·82 to 0·28)
Fatigue Severity Scale	37·4	29·7 (25·6 to 33·7)	29·9 (25·8 to 33·9)	–0·2 (–3·3 to 2·9)
Timed-stands test, s	37·3	25·4 (21·8 to 29·0)	26·0 (22·4 to 29·6)	–0·6 (–2·4 to 1·2)
Medical Outcomes Study Short Form-36 Questionnaire				
Physical functioning	53·8	71·9 (64·0 to 79·8)	67·7 (60·0 to 75·5)	4·2 (–2·6 to 10·9)
Role–physical	41·2	66·5 (54·0 to 78·9)	59·5 (47·4 to 71·7)	6·9 (–6·1 to 20·0)
Bodily pain	53·3	68·9 (61·6 to 76·2)	65·0 (57·8 to 72·2)	3·9 (–1·8 to 9·5)
Social functioning	57·9	79·4 (72·5 to 86·3)	75·8 (69·1 to 82·5)	3·6 (–4·2 to 11·3)
Mental health	61·6	72·4 (66·8 to 78·0)	70·4 (64·9 to 75·8)	2·0 (–3·0 to 7·1)
Role–emotional	48·5	72·8 (61·8 to 83·8)	72·8 (62·1 to 83·6)	0·0 (–11·3 to 11·2)
Vitality	39·0	55·7 (48·9 to 62·5)	51·9 (45·3 to 58·5)	3·8 (–3·1 to 10·8)
General health	50·6	57·5 (50·4 to 64·6)	56·3 (49·2 to 63·4)	1·2 (–2·8 to 5·3)

*Values are adjusted means from a mixed-effects analysis of variance model that includes fixed effects for treatment and period and a random effect for participant. Numbers of participants contributing to the analysis of each outcome: Interactive voice response-diary stiffness score—mexiletine (n=49), lamotrigine (n=51); Myotonia Behaviour Score—mexiletine (n=48), lamotrigine (n=51); Brief Pain Inventory pain scores—mexiletine (n=42), lamotrigine (n= 46); Brief Pain Inventory pain interference—mexiletine (n=43), lamotrigine (n=46); Fatigue Severity Scale—mexiletine (n=44), lamotrigine (n=46); Timed stands test—mexiletine (n=44), lamotrigine (n=47); Medical Outcomes Study Short Form-36 Questionnaire subscale scores—mexiletine (n=43), lamotrigine (n=46).

Table 2: **Treatment differences on primary and secondary outcome variables**

37 participants had at least one adverse event (table 3). The most common adverse events were indigestion–reflux (eight participants, 208 participant-days receiving mexiletine; seven participants, 130 participant-days receiving lamotrigine). Most participants tolerated the discomfort, with one participant taking mexiletine requiring treatment with omeprazole intermittently. The next most common adverse events were headache (four participants on each treatment), followed by palpitations (three participants receiving mexiletine, two participants receiving lamotrigine) and mood changes (five participants receiving mexiletine). Mood changes were mostly anxiety and low mood usually experienced in combination and not requiring any specific treatment. Palpitations were brief and mild, and reported in retrospect. No participants required presentation to hospital or general practice for review of palpitations or cardiac symptoms. Two participants

	Mexiletine, n (% of those exposed)	Duration of symptoms, participant-days	Lamotrigine, n (% of those exposed)	Duration of symptoms, participant-days
Indigestion–reflux	8 (15%)	208	7 (14%)	130
Headache	4 (7%)	91	4 (8%)	101
Mood changes	5 (9%)	60	0	0
Palpitations	3 (6%)	35	2 (4%)	18
Nausea	1 (2%)	14	2 (4%)	28
Tremor	1 (2%)	42	2 (4%)	34
Brain fog	2 (4%)	21	0	0
Dry mouth	0	0	2 (4%)	31
Insomnia	2 (4%)	98	0	0
Lethargy	1 (2%)	4	1 (2%)	14
Stomachache	2 (4%)	98	0	0
Constipation	1 (2%)	7	0	0
Double vision	0	0	1 (2%)	1
Drowsy	1 (2%)	7	0	0
Rash	1 (2%)	1	0	0
Stiffness	1 (2%)	1	0	0
Vomiting	0	0	1 (2%)	4
Weight gain	1 (2%)	7	0	0
Weight loss	0	0	1 (2%)	28

Table 3: **Adverse events by treatment condition**

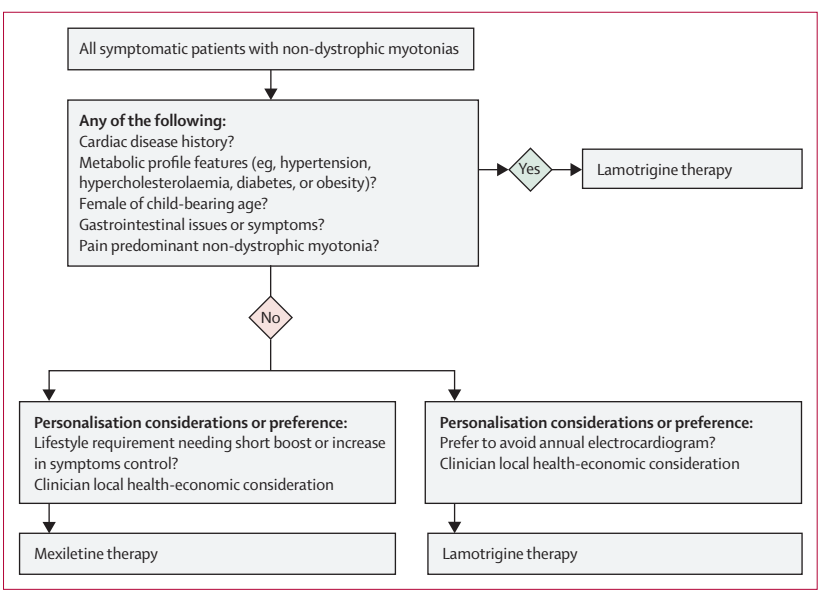

Figure 3: **Personalised treatment algorithm**
The treatment algorithm is based on results from this trial combined with pharmocodynamic and pharmacokinetic properties, side-effect profiles of lamotrigine and mexiletine, and local economic considerations (eg, cost of the drug to the health service). The personalised considerations and preferences prescribe a personalised treatment approach whereby a patient might prefer the quick-acting dynamics of mexiletine versus the slow uptitration of lamotrigine. By contrast, other patients might prefer a stable therapeutic concentration achieved with lamotrigine or prefer to avoid the inconvenience of annual cardiac surveillance. Similarly the local costs of mexiletine to the national health system should be considered.

receiving mexiletine had insomnia lasting 98 days in total. Two participants who were receiving mexiletine had stomachache lasting 98 days in total. No patients who were receiving lamotrigine had rash and no severe rashes were seen. No severe adverse events were reported.

46 participants completed the blindedness questionnaire, the results of which are presented in the appendix (p 3). Of those who offered a guess with respect to their treatment sequence, eight guessed correctly in the mexiletine–lamotrigine sequence and nine guessed correctly in the lamotrigine–mexiletine sequence. There was no evidence of an association between the guessed sequence and the actual sequence (p=0·93, Fisher's exact test).

The medication choice after the trial was completed was also recorded for 47 participants. 30 participants (64%) commenced lamotrigine post-trial, 13 (43%) of whom were receiving mexiletine, 14 (47%) of whom were receiving no treatment, two (7%) of whom were receiving lamotrigine, and one (<1%) of whom was receiving acetazolamide before commencing the trial. 17 participants (36%) commenced mexiletine treatment post-trial, 12 (71%) of whom were receiving mexiletine and five (29%) of whom were receiving no treatment before commencing the trial.

In period 1 there was 96% compliance with dosing (doses taken per doses scheduled; 96% with mexiletine and 97% with lamotrigine) and in period 2, there was an average of 98% compliance with dosing (98% with mexiletine and 97% with lamotrigine).

Discussion

In this non-inferiority trial, using the primary outcome measure of the mean IVR-diary stiffness score, we did not show that lamotrigine is non-inferior to mexiletine for patients with non-dystrophic myotonias. A comparison of means from baseline showed a substantial improvement in all outcomes with both mexiletine and lamotrigine treatment, showing similar efficacy and supporting previous efficacy trials of these agents. No severe adverse effects were seen.

The treatment differences in mean responses for pain and fatigue outcomes in particular were quite small. Pain and fatigue are major components of non-dystrophic myotonia and have a large effect on employment and function.[26] Lamotrigine is often effective for other forms of chronic neuropathic pain management.[27,28] Additional secondary effects of lamotrigine might also extend to mood stabilisation benefits, because it is also prescribed for this indication. Such secondary benefits will require evaluation with prospective data collection in a large dataset. Lamotrigine might also be an option for paediatric patients with myotonia, because it has a long history of safe use in epilepsy in this population.

The only previous randomised controlled trial of lamotrigine compared with placebo for non-dystrophic myotonias consisted of 26 participants. Our study, with

53 participants, additionally suggests efficacy in these rare diseases. For mexiletine, there are now several trials showing efficacy. Our trial provides a head-to-head comparison of these agents, which can be used to inform clinical decisions. Amalgamation of trial outcomes and adverse events enabled us to provide a clinical treatment algorithm for non-dystrophic myotonias. The algorithm is a personalised therapy approach, tailored to patient characteristics, clinical features, and comorbidities (as illustrated in figure 3). This algorithm suggests lamotrigine as first-line therapy for patients with contraindications to mexiletine, such as cardiac disease, and those susceptible to side-effects of mexiletine, such as patients with gastrointestinal issues. Additionally, given that non-dystrophic myotonias are a lifelong condition, lamotrigine is better suited for patients who are at risk of developing cardiac disease in the future—ie, patients with a metabolic profile (hypertension, hypercholesterolaemia, diabetes, and obesity). Similarly, lamotrigine is more suitable for women of child-bearing age who might want to consider remaining on antimyotonic treatment during pregnancy when symptoms might worsen. Patients with more pain might benefit more so from lamotrigine, making it more suitable as a first-line agent.

In addition to adverse events and clinical characteristics, a consideration in this approach is the medication mode of action. Mexiletine has a quick onset of action, with most patients noticing benefit within 30–40 min and a short half-life of 10 h.[29] In contrast, lamotrigine requires a slow up-titration to minimise the risk of a rash and the half-life ranges from 24·1 h to 35 h.[30] These differences in mode of action translate to differences in the experience of symptomatic treatment. For some patients, a quick onset boost or increase in symptomatic control before exercise or other activity is preferred; hence, they might be more suited to mexiletine. On the other hand, accidental omission of a dose leads to significant noticeable symptoms with mexiletine, although this is much less of an issue with lamotrigine, for which a serum concentration is achieved and longer duration of washout is needed. Other considerations include the annual need for cardiac surveillance with mexiletine treatment.

An important consideration is the relative cost–benefit of symptomatic treatment. In the UK and Europe, mexiletine is available as an indication for treatment of myotonia in non-dystrophic myotonias. Locally in the UK, mexiletine is available at a cost of £875 (excluding VAT) for 100 capsules, with an indicative annual cost per patient to the National Health Service (NHS) of £9450 (at the standard dose of mexiletine 167 mg three times daily). Lamotrigine has a cost of £2·25 (excluding VAT) for 56 capsules, with an indicative annual cost per patient to the NHS of £28·93 (at the higher dose of lamotrigine 200 mg twice daily). With a £9421·07 per annum per patient cost disparity and similar antimyotonic effects of mexiletine and lamotrigine, a formal prospective cost–benefit analysis appears to be warranted to review industry pricing of mexiletine.

Given clinical equipoise before these trial results, at trial completion, participants returned to clinical treatment as per their preference. Of the 25 participants who had been receiving mexiletine pretrial, 13 (52%) changed to lamotrigine, with the most frequent reason for the change being adverse events of mexiletine. One participant's additional reason to change to lamotrigine was ease of access, and for six participants, efficacy of lamotrigine was the motivation to change.

Our trial is based on validated patient-reported outcomes, which capture the effect of myotonia on patients and allow meaningful translation of trial results to patient care. Despite this trial selecting for patients with less severe clinical symptoms, the baseline mean scores were still relatively high (IVR-diary stiffness score 5·30 out of 9; MBS 2·93 out of 5), reflecting a known need for treatment in non-dystrophic myotonias. Moreover, the trial cohort was young, with age of onset generally in the first decade, reflecting the marked effect of non-dystrophic myotonias on education and employment and the need for therapy.

We show that it is clinically feasible to do head-to-head clinical trials to directly inform clinical practice in rare neurological conditions. Head-to-head trials are not often done in neuromuscular conditions, making informed clinical decision-making challenging. We did not encounter any difficulty with unmasking, with no association detected between the guessed and actual treatment sequences. Only one participant selected "Very sure" regarding their guess and the participant guessed incorrectly. The fact that we have not encountered potential unmasking speaks also to the similar amounts of improvement between the two test medications. There was no evidence of a treatment-by-period interaction, although the power to detect such an interaction is notoriously low.[23]

All travel was reimbursed in this trial and the trial was advertised to our patients throughout the UK; however, the majority of the cohort was White, reflecting the need to strengthen diversity in research engagement. Further limitations in our trial include the number of withdrawals (14 [23%] of 60), which was somewhat higher than anticipated. The trial is biased towards excluding patients with more severe myotonia. Three participants with more severe myotonia withdrew on the lower dosage up-titration regimen. This is likely to be a key issue with future symptomatic treatment trials in non-dystrophic myotonia now that two effective therapies for myotonia exist. Patients are unlikely to readily stop effective, symptomatic, and well tolerated therapy. It is possible that further trials will need to focus on non-responders to either medication or add-on therapies. Alternative sodium channel blockers such as flecainide and ranolazine have shown promise in small series and preclinical work, and might be potential add-on approaches or additional personalised approaches for

non-responders. Prospective data collection is required to further understand characteristics and clinical features, as well as genotypes of non-responders to mexiletine and lamotrigine.

Complementing the clinical characterisation is the electrophysiological and functional characterisation. Mexiletine binds with affinity to inactivated channels creating a use-dependent block of sodium channels. In contrast, lamotrigine blocks the 1·4 subunit and prolongs the refractory period. Flecainide also binds to inactive sodium channels, but differences in the use-dependence block translate into differences in clinical response between mexiletine and flecainide.[16] Further understanding of the functional interaction with sodium channel blockers will allow further personalisation of the treatment algorithm.

Amalgamating treatment benefits as well as a head-to-head comparison of adverse events and pharmacokinetics has enabled us to suggest a personalised treatment algorithm for patients with non-dystrophic myotonias. With two effective therapies for symptomatic treatment of myotonia, future therapy development for myotonia is likely to be directed to non-responders or to patients with more severe clinical manifestations for whom add-on therapies might be necessitated.

Contributors

VV was the chief investigator, attained grant funding, and wrote the first draft with input from MPM. MPM did the statistical analysis. EM and MGH contributed to grant acquisition. IS, DLJ, EM, RJB, MPM, and MGH reviewed the manuscript. All authors had access to all study data if requested. VV and MPM have directly accessed and verified the data reported in this manuscript. VV, MM, and MGH were responsible for the decision to submit the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified metadata can be made available on reasonable request to the corresponding author.

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References

1 Vivekanandam V, Jaibaji R, Sud R, et al. Prevalence of genetically confirmed skeletal muscle channelopathies in the era of next generation sequencing. *Neuromuscul Disord* 2023; **33:** 270–73.
2 Cannon SC. Pathomechanisms in channelopathies of skeletal muscle and brain. *Annu Rev Neurosci* 2006; **29:** 387–415.
3 Cannon SC. Voltage-sensor mutations in channelopathies of skeletal muscle. *J Physiol* 2010; **588:** 1887–95.
4 Lossin C, George AL. Myotonia congenita, chapter 2. In: Hall, JC, Dunlap JC, Friedman T, van Heyningen V, eds. Advances in genetics, vol 63. San Diego, CA, USA: Elsevier, 2008: 25–55.
5 Sansone VA, Ricci C, Montanari M, Apolone G, Rose M, Meola G. Measuring quality of life impairment in skeletal muscle channelopathies. *Eur J Neurol* 2012; **19:** 1470–76.
6 Vivekanandam V, Minuot P, Hanna MG, Matthews E. Skeletal muscle channelopathies. *Neurol Clin* 2020; **38:** 481–91.
7 Raja Rayan DL, Hanna MG. Managing pregnancy and anaesthetics in patients with skeletal muscle channelopathies. *Neuromuscul Disord* 2020; **30:** 539–45.
8 Statland JM, Bundy BN, Wang Y, et al. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *JAMA* 2012; **308:** 1357–65.
9 Stunnenberg BC, Raaphorst J, Groenewoud HM, et al. Effect of mexiletine on muscle stiffness in patients with nondystrophic myotonia evaluated using aggregated n-of-1 trials. *JAMA* 2018; **320:** 2344–53.
10 Vicart S, Franques J, Bouhour F, et al. Efficacy and safety of mexiletine in non-dystrophic myotonias: a randomised, double-blind, placebo-controlled, cross-over study. *Neuromuscul Disord* 2021; **31:** 1124–35.
11 Suetterlin KJ, Bugiardini E, Kaski JP, et al. Long-term safety and efficacy of mexiletine for patients with skeletal muscle channelopathies. *JAMA Neurol* 2015; **72:** 1531–33.
12 Gascon GG, Staton RD, Patterson BD, et al. A pilot controlled study of the use of imipramine to reduce myotonia. *Am J Phys Med Rehabil* 1989; **68:** 215–20.
13 Durelli L, Mutani R, Fassio F. The treatment of myotonia: evaluation of chronic oral taurine therapy. *Neurology* 1983; **33:** 599–603.
14 Finlay M. A comparative study of disopyramide and procainamide in the treatment of myotonia in myotonic dystrophy. *J Neurol Neurosurg Psychiatry* 1982; **45:** 461–63.
15 Kwieciński H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. *Acta Neurol Scand* 1992; **86:** 371–75.
16 Desaphy JF, Altamura C, Vicart S, Fontaine B. Targeted therapies for skeletal muscle ion channelopathies: systematic review and dsteps towards precision medicine. *J Neuromuscul Dis* 2021; **8:** 357–81.
17 Andersen G, Hedermann G, Witting N, Duno M, Andersen H, Vissing J. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study. *Brain* 2017; **140:** 2295–305.
18 Hammarén E, Kjellby-Wendt G, Lindberg C. Quantification of mobility impairment and self-assessment of stiffness in patients with myotonia congenita by the physiotherapist. *Neuromuscul Disord* 2005; **15:** 610–17.
19 Sealed Envelope. 2022. Simple randomisation service. https://www.sealedenvelope.com/simple-randomiser/v1/ (accessed May 22, 2021).
20 Statland JM, Wang Y, Richesson R, et al. An interactive voice response diary for patients with non-dystrophic myotonia. *Muscle Nerve* 2011; **44:** 30–35.
21 Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the brief pain inventory for chronic nonmalignant pain. *J Pain* 2004; **5:** 133–37.
22 Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993; **306:** 1437–40.
23 Senn S. Cross-over trials in clinical research, 2nd edn. Chichester, UK: John Wiley & Sons, 2002: pp 89–143.
24 Little RJA, Rubin DB. Statistical analysis with missing data, 2nd edn. Hoboken, NJ: John Wiley & Sons, 2002: pp 221–52.
25 Jones B, Kenward M. Design and analysis of cross-over trials, 2nd edn. Boca Raton, FL: CRC Press, 2003.
26 Vivekanandam V, Jayaseelan D, Hanna MG. Muscle channelopathies, chapter 21. In: Younger DS, ed. Handbook of clinical neurology. Amsterdam: Elsevier, 2023: 521–32.
27 Liampas A, Velidakis N, Georgiou T, et al. Prevalence and management challenges in central post-stroke neuropathic pain: a systematic review and meta-analysis. *Adv Ther* 2020; **37:** 3278–91.
28 Lambru G, Zakrzewska J, Matharu M. Trigeminal neuralgia: a practical guide. *Pract Neurol* 2021; **21:** 392–402.
29 Woosley RL, Wang T, Stone W, et al. Pharmacology, electrophysiology, and pharmacokinetics of mexiletine. *Am Heart J* 1984; **107:** 1058–65.
30 Garnett WR. Lamotrigine: pharmacokinetics. *J Child Neurol* 1997; **12** (suppl 1): S10–15.