PRELIMINARY COMMUNICATION

Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia

A Randomized Controlled Trial

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Context Nondystrophic myotonias (NDMs) are rare diseases caused by mutations in skeletal muscle ion channels. Patients experience delayed muscle relaxation causing functionally limiting stiffness and pain. Mexiletine-induced sodium channel blockade reduced myotonia in small studies; however, as is common in rare diseases, larger studies of safety and efficacy have not previously been considered feasible.

Objective To determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDMs.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled 2-period crossover study at 7 neuromuscular referral centers in 4 countries of 59 patients with NDMs conducted between December 23, 2008, and March 30, 2011, as part of the National Institutes of Health–funded Rare Disease Clinical Research Network.

Intervention Oral 200-mg mexiletine or placebo capsules 3 times daily for 4 weeks, followed by the opposite intervention for 4 weeks, with 1-week washout in between.

Main Outcome Measures Patient-reported severity score of stiffness recorded on an interactive voice response (IVR) diary (scale of 1 = minimal to 9 = worst ever experienced). Secondary end points included IVR-reported changes in pain, weakness, and tiredness; clinical myotonia assessment; quantitative measure of handgrip myotonia; and Individualized Neuromuscular Quality of Life summary quality of life score (INQOL–QOL, percentage of maximal detrimental impact).

Results Mexiletine significantly improved patient-reported severity score stiffness on the IVR diary. Because of a statistically significant interaction between treatment and period for this outcome, primary end point is presented by period (period 1 means were 2.53 for mexiletine and 4.21 for placebo; difference, –1.68; 95% CI, –2.66 to –0.706; $P < .001$; period 2 means were 1.60 for mexiletine and 5.27 for placebo; difference, –3.68; 95% CI, –3.85 to –0.139; $P = .04$). Mexiletine improved the INQOL–QOL score (mexiletine, 14.0 vs placebo, 16.7; difference, –2.69; 95% CI, –4.07 to –1.30; $P < .001$) and decreased handgrip myotonia on clinical examination (mexiletine, 0.164 seconds vs placebo, 0.494 seconds; difference, –0.330; 95% CI, –0.633 to –0.142; $P < .001$). The most common adverse effect was gastrointestinal (9 mexiletine and 1 placebo). Two participants experienced transient cardiac effects that did not require stopping the study (1 in each group). One serious adverse event was determined to be not study related.

Conclusion In this preliminary study of patients with NDMs, the use of mexiletine compared with placebo resulted in improved patient-reported stiffness over 4 weeks of treatment, despite some concern about the maintenance of blinding.

Trial Registration clinicaltrials.gov Identifier: NCT00832000

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THE NONDYSTROPHIC MYOTONIAS (NDMs) are rare disorders (prevalence 1:100 000[1]) caused by mutations in skeletal muscle chloride and sodium channels with the common clinical feature of myotonia without muscle wasting.[2] Myotonia causes functionally limiting stiffness, pain, fatigue, and weakness. Data on treatment of NDMs are largely anecdotal, consisting of case series and a single-blind, controlled trial of quinine,[3] procainamide,[3,4] phenytoin,[4] tocainide,[5] and mexiletine.[6,7] A 2006 Cochrane review[8] concluded there were not sufficient data to consider any treatment safe and effective for myotonia.

For editorial comment see p 1377.

Mexiletine is a class 1b antiarrhythmic medication with a high affinity for muscle sodium channels. In vitro and animal models suggest mexiletine reduces muscle fiber excitability caused

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by common NDM mutations.[9-12] A recent randomized controlled, crossover study showed mexiletine to be effective for reducing myotonia in patients with myotonic dystrophy type 1.[13]

A major impediment to randomized controlled trials in NDM is its rarity. The National Institutes of Health–funded Rare Disease Clinical Research Network (RDCRN) was designed to provide centralized infrastructure for investigations of rare diseases. In a natural history study, we used a novel interactive voice response (IVR) diary of patient symptoms and found stiffness was the most common and severe symptom reported in NDMs regardless of mutation.[14] Herein, we report a phase 2 international randomized, placebo-controlled, crossover study of mexiletine in NDMs using the RDCRN and patient-reported stiffness severity score on the IVR diary as the primary outcome.

METHODS

Trial Design

We conducted a randomized, double-blind, placebo-controlled, 2-period crossover trial at 7 centers in 4 countries (United States, Canada, England, and Italy). Treatment periods were 4 weeks in duration, separated by a 1-week washout period. The trial was approved by the institutional review boards at the 7 centers, and written informed consent was obtained from all participants. The National Institutes of Health established a data and safety monitoring board, which met every 6 months.

Participants

Eligible participants were aged at least 16 years, had clinical symptoms or signs of NDMs, and had myotonic potentials on electromyography. Participants were enrolled in the Consortium for Clinical Investigation of Neurologic Channelopathies NDM Natural History Study, or were a new patient with genetically confirmed NDMs, or had clinical features of NDMs but negative myotonic dystrophy DNA testing. Patients taking antimyotonic agents were required to discontinue medications for a washout period equal to 7 times the half-life of elimination before their baseline visit. Participants were ineligible if they had specific contraindications to taking mexiletine (cardiac conduction defects, hepatic or renal disease, or heart failure).

The trial was registered with clinicaltrials.gov (NCT00721942) in July 2008. Due to a duplicate registration number, records were consolidated in January 2009 (NCT00832000). The study was conducted between December 23, 2008, and March 30, 2011 (first patient enrolled December 23, 2008) at 7 RDCRN/Consortium for Clinical Investigation of Neurologic Channelopathies sites (University of Kansas Medical Center, Kansas City; University of Rochester Medical Center, Rochester, New York; Brigham and Women's Hospital, Boston, Massachusetts; University of Texas Southwestern, Dallas; London Health Sciences Center, London, Ontario, Canada; Medical Research Council for Neuromuscular Diseases, University College London Institute of Neurology, London, England; and the University of Milan, Istituti di Ricovero e Cura a Carattere Scientifico Policlinico San Donato, Milan, Italy).

Interventions

Participants were randomized to either 200-mg capsules of mexiletine 3 times a day or 200-mg capsules of placebo 3 times a day for 4 weeks. After a 1-week washout period, the participants were administered the opposite intervention for 4 weeks.

Mexiletine was purchased from TEVA Pharmaceutical. The placebo was microcrystalline cellulose (Avicel PH 102). The mexiletine and placebo were encapsulated at the University of Iowa Research Pharmacy (Iowa City) with Swedish orange capsule. A qualified person from Brecon inspected TEVA and the University of Iowa Research Pharmacy for the purpose of the European directive. Mexiletine drug level testing was performed at Mayo Medical Laboratory (Rochester, Minnesota). Random drug levels were collected before study visits at baseline and the end of weeks 4, 5, and 9.

Outcome Measures

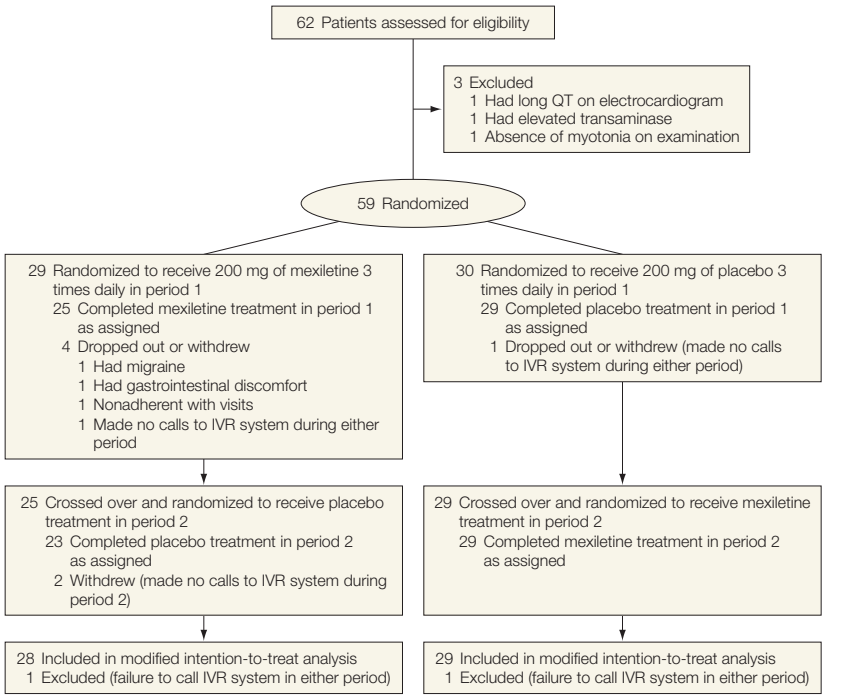
Baseline characteristics included sex, age, and self-reported race/ethnicity. For the IVR diary, telephone calls were made daily for the entire 9-week study. All other outcome measurements were performed at baseline, the end of each treatment period, and the end of washout.

Primary End Points. The primary end point was defined as the severity score of stiffness reported by participants during the third and fourth week of each treatment period via the IVR diary. Participants called in to report symptom severity on a scale of 1 to 9, with 1 being minimal and 9 being the worst ever experienced (no symptom=0 for analysis) (eFigure, available at http://www.jama.com).[14]

Secondary End Points. Secondary end points included (1) participant-assessed pain, weakness, and tiredness as measured by the IVR diary from daily telephone calls made over the last 2 weeks of each period.[14] (2) 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 them). Five trials of each maneuver were performed in sequence at each visit and the time was measured by a stopwatch. (3) A quantitative measure of handgrip myotonia was obtained using a commercially available grip dynamometer and computerized 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.[15,16] (4) The maximal postexercise decrement in compound muscle action potential after short and long exercise was determined as previously described.[17,18] (5) Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti

minimi and right tibialis anterior.[19] (6) Patients filled out the 36-Item Short-Form Health Survey (SF-36) and the Individualized Quality of Life questionnaire for neuromuscular disorders (INQOL).[20-22] The INQOL is composed of 10 sections (muscle locking, weakness, pain, fatigue, activities, social relationships, independence, emotions, body image, and effects of treatment) and a summary QOL score (INQOL–QOL).

Figure 1. Study Design and Disposition of Patients



IVR indicates interactive voice response.

Sample Size

The sample size goal was set to 54 participants with available primary end point measurements for both treatment periods. This sample size, determined by computer simulation, provided at least 93% power to detect an effect size of one-quarter of an SD (within-participant) in the primary end point with a 2-sided hypothesis test and an $\alpha = .05$. The variation in power was due to varying the degree of between-participant SD; larger SDs lowered the power since the effect in the active treatment period for low-severity scores cannot be less than 0. The simulations were based on 500 Monte Carlo realizations, a mean for the placebo group of 3, a within-participant SD of 1.5, and a between-participant SD ranging from 1.5 to 3.0. The effect size of one-quarter of an SD was chosen to be conservative given the tentative assumptions in the simulation, to compensate for the unknown degree of participant adherence to treatment, and to have a sufficient sample size available for the secondary IVR diary end points for which some participants do not have the symptom.

Randomization and Blinding

Participants were randomly assigned the order of the 2 treatments in a 1:1 ratio, stratified by institution. Randomization was performed centrally at the data management coordinating center (University of South Florida, Tampa) using a computer-generated permuted block structure, initially with a block size of 4 then, toward the end of the trial, switching to a block size of 2. 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. Participants, physicians, and evaluators were blinded to medication assignment.

Statistical Analysis

Our study used the intention-to-treat principle modified to remove missing values that were assumed to be missing at random. All treatment effect analyses used the linear mixed-effects model (random effect for participant, independent and identically distributed random errors within participant) to adjust for any period effect and include data from dropouts.[23-25] One assumption required to produce valid Wald tests is that the residuals be normally distributed. To fulfill this assumption, the daily reported IVR severity scores (involving the 4 end points of stiffness, pain, tiredness, and weakness) were replaced with the weekly means, and QQ plots confirmed that this assumption was satisfied. Another assumption when modeling crossover study data and including only the main effects for period and treatment is that the treatment effect is the same across periods. The lack of consistency is often referred to as a "carryover" effect, although this term can be a misnomer.[26]

For the primary end point, the Wald test of the treatment-sequence group variable (treatment group) was significant (estimate, 0.997; $P = .04$). This result does not necessarily indicate that the second period data are invalid and should be ignored.[25,27] However, it may indicate that the treatment effect in period 2 is biased and that the additive model may yield biased estimates. A fair presentation of the results is to include an interaction term for period 2 and treatment, in order to present the treatment effect estimates separately by period. The test for "carryover" effect was

considered significant if $P<.10$.[24] Significance was detected for 4 of the subscales of the SF-36: vitality, emotional role, mental health, and mental composite. Thus, these results and stiffness are displayed by period. The significance level displayed for period 2 is from the Wald test associated with the interaction term of period 2 and mexiletine and not the entire treatment effect, and the significance level displayed for period 1 is from the test of the main effect term for treatment variable. Most of the CIs were computed in the usual way using the SE of the estimate taken from the model results; the exceptions were the end points requiring a log transformation for which a bootstrap CI was computed. The effect size was the treatment effect estimate divided by the within-participant SD.

To test whether the overall treatment effect varies within mutation class, we used the log likelihood test contrasting the model with vs without the treatment and mutation class interaction terms as a homogeneity test.

For the electrographic myotonia assessment, the score was converted to a numeric value (absent = 0, 1+ = 1, 2+ = 2, and 3+ = 3). The end point was the sum of the numerical scores of the 2 muscles. Although the mixed model was used to provide mean estimates, the paired Wilcoxon test was used to test the treatment effect hypothesis. To fulfill the normality assumption for the clinical handgrip and eye closure times, we applied the following transformation: $\log(t_i+0.1)$. Similarly, quantitative handgrip myometry required a log (t_i) transformation; the model included a linear term for grip sequence number and a nested random effect for trial number.

All *P* values were 2-sided and .05 was considered the threshold of statistical significance for all tests except for the carryover effect. Because this trial identified a primary end point, all other *P* values presented were for secondary end points and are not adjusted for multiple testing. Analysis was performed using TIBCO Spotfire S+ version 8.1 (TIBCO Software Inc).

Table 1. Screening Baseline Characteristics of the 2 Treatment Sequence Groups[a]

Characteristics	Treatment Sequence: Mexiletine Then Placebo (n = 29)	Treatment Sequence: Placebo Then Mexiletine (n = 30)
Age, mean (range), y	41.1 (16-66)	44.7 (22-68)
Male sex	13 (44.8)	20 (66.7)
White race[b]	28 (96.6)	29 (100.0)
Hispanic ethnicity	4 (13.8)	9 (30.0)
Medication		
Mexiletine	7 (24.1)	6 (20.0)
Other	3 (10.3)	1 (3.3)
IVR diary–stiffness, mean (SD)[c]	3.89 (2.39)	4.63 (2.99)
SF-36, mean (SD)		
Physical, norm-based	38.7 (9.65)	40.8 (11.0)
Mental component	44.5 (13.3)	47.6 (9.8)
INQOL–QOL score, mean (SD)[d]	14.0 (9.03)	15.9 (12.5)
Geometric-like mean (pseudo SD), s[e]		
Clinical hand-opening time	1.11 (0.898-3.48)	0.605 (0.510-1.84)
Clinical eye-opening time	0.507 (0.486-2.42)	0.466 (0.455-2.31)
Quantitative handgrip myotonia	0.651 (0.288-0.518)	0.507 (0.211-0.361)
Electromyographic grade = 3+[d]		
Abductor digiti minimi	18 (62.1)	18 (62.1)
Tibialis anterior	20 (69.0)	19 (65.5)
Short exercise test (% of baseline), mean (SD)[d]	78.7 (24.5)	80.8 (28.7)
Mutation		
Chloride	17 (58.6)	17 (56.7)
Sodium	10 (34.5)	11 (36.7)
None identified	2 (6.9)	2 (6.7)

Abbreviations: INQOL–QOL, Individualized Neuromuscular Quality of Life–Quality of Life; IVR, interactive voice response; SF-36, 36-Item Short-Form Health Survey.

[a] Data are shown as No. (%) unless otherwise specified. Reference ranges for the scales used are as follows: IVR diary (0 = no symptom, 1 = minimal, 9 = worst ever experienced[14]); SF-36 Physical and Mental composite (a linear T-score transformation 0-100 scale with US mean score = 50, lower score = larger impact[22]); INQOL scores (percentage of the maximum detrimental impact, a higher score indicates greater impact, with the exception of treatment effects, where a higher score indicates perceived effectiveness[20]); clinical hand-opening and eye-opening time increased with increasing myotonia; electromyographic grade (ranges from 0 for no myotonia, 1+ for meeting minimal electrographic criteria for myotonia to 3+ for myotonia in every needle position[19]); the % of baseline on short exercise testing will decrease with increasing myotonia[18]; and quantitative handgrip myotonia evaluation is expected to increase with increasing myotonia.[15]

[b] One participant declined reporting race.

[c] Eight participants had a true baseline report of stiffness severity. Consequently, if unreported, day 1 report was used (40) and if that was unreported, day 2 report was used (10).

[d] One participant was missing from each of the QOL scores, the abductor digiti minimi and tibialis anterior electromyographic grades, and the short exercise test results.

[e] Geometric-like mean is the inverse transformation (exp[y]-0.1) of the mean of transformed (log[t+0.1]) times. The pseudo SDs are the widths of the inverse transformed interval between the mean and ±1 SD from the mean; these being calculated on the transformed scale. Eight participants did not have baseline quantitative handgrip myotonia test results. None were missing for the clinical tests.

RESULTS

Participant Flow

Eligible participants were recruited between December 23, 2008, and January 25, 2011. Of 62 participants recruited, 3 were ineligible (1 had a prolonged QTc at screening visit, 1 had elevated transaminase levels, and 1 had no clinical myotonia on examination). Fifty-nine participants were randomized to receive either study medication or placebo. Two participants did not make expected telephone calls to the IVR diary system during weeks 3 to 4 of either period. There were 3 dropouts (1 secondary to migraine headaches, 1 secondary to gastric discomfort, and 1 for failure to comply with study visits). An additional 2 participants did not make telephone calls to the IVR diary system during weeks 3 to 4 of the second period, so only provided data for period 1 (FIGURE 1).

Table 2. Mixed Model Results Including Mean Estimate Under Both Treatments, the Difference of Treatments (Mexiletine Minus Placebo), Effect Size, and Significance Level[a]

End Point	No. of Participants	Mean (95% CI)		Treatment Effect Estimate (95% CI)	Effect Size	*P* Value
		Mexiletine Treatment	Placebo Treatment			
Interactive voice response						
Stiffness, first period[b]	57	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)	–1.68 (–2.66 to –0.706)	–1.36	<.001
Stiffness, second period[b]	57	1.60 (1.04 to 2.20)	5.27 (4.44 to 6.27)	–3.68 (–3.85 to –0.139)	–2.97	.04
Pain, overall[c]	48	1.54 (0.924 to 2.13)	3.17 (2.43 to 3.93)	–1.63 (–2.00 to –1.26)	–1.36	<.001
Weakness, overall[c]	44	1.96 (1.42 to 2.63)	3.22 (2.52 to 3.98)	–1.26 (–1.67 to –0.861)	–0.994	<.001
Tiredness, overall[c]	49	2.9 (2.12 to 3.68)	3.82 (3.03 to 4.53)	–0.918 (–1.30 to –0.532)	–0.709	<.001
Exercise (% baseline)						
Short, overall	56	83.1 (77.5 to 88.4)	78.6 (71.9 to 84.7)	4.54 (–0.680 to 9.75)	0.347	.09
Prolonged, overall	56	81.8 (76.8 to 87.0)	80.1 (74.7 to 86.4)	1.69 (–3.34 to 6.73)	0.134	.50
Needle electromyography						
RADM, overall	56	2.05 (1.75 to 2.33)	2.62 (2.39 to 2.86)	–0.568 (–0.812 to –0.325)	–0.947	<.001
RTA, overall	56	2.07 (1.73 to 2.37)	2.54 (2.28 to 2.76)	–0.464 (–0.675 to –0.254)	–0.900	<.001
SF-36						
Physical function, overall	57	42.8 (40.1 to 46.1)	37.8 (34.9 to 41.3)	5.00 (2.81 to 7.20)	.904	<.001
Role physical, overall	57	46.5 (43.6 to 49.2)	39.2 (35.7 to 42.6)	7.23 (4.55 to 9.92)	1.07	<.001
Bodily pain, overall	57	49.8 (46.4 to 52.6)	42.0 (38.6 to 45.5)	7.78 (5.08 to 10.5)	1.14	<.001
General health, overall	57	45.5 (41.9 to 48.7)	44.5 (41 to 47.7)	0.977 (–0.659 to 2.61)	0.240	.24
Vitality, first period	57	45.5 (41.1 to 49.6)	43.7 (39.7 to 48.1)	1.76 (–4.34 to 7.85)	0.211	.57
Vitality, second period	57	51.9 (48.1 to 55.5)	40.0 (35.1 to 45.0)	11.9 (–0.307 to 20.5)	1.43	.06
Social function, overall	57	47.1 (44.4 to 49.8)	41.9 (38.5 to 44.9)	5.27 (2.69 to 7.85)	0.809	<.001
Role emotional, first period	57	46.2 (42.0 to 50.3)	45.5 (41.2 to 49.4)	0.764 (–5.68 to 7.21)	0.102	.81
Role emotional, second period	57	49.9 (46.2 to 53.1)	39.1 (33.5 to 45.0)	10.8 (–1.51 to 21.6)	1.45	.09
Mental health, first period	57	47.3 (43.6 to 51.0)	47.3 (43.7 to 50.6)	0.016 (–5.24 to 5.27)	0.00258	.99
Mental health, second period	57	53.3 (50.2 to 56.2)	44.4 (39.8 to 48.7)	8.84 (–0.572 to 18.2)	1.42	.07
Physical composite, overall	57	44.8 (41.9 to 47.4)	39.2 (35.9 to 41.9)	5.58 (3.44 to 7.72)	1.04	<.001
Mental composite, first period	57	47.4 (44.0 to 50.2)	47.7 (44.2 to 51.3)	–0.351 (–5.87 to 5.17)	–0.0539	.90
Mental composite, second period	57	53.1 (50.3 to 55.8)	42.7 (36.8 to 48.3)	10.4 (0.941 to 20.6)	1.60	.03
INQOL						
Weakness, overall	35	45.7 (37.7 to 52.6)	49.3 (41.7 to 57.3)	–3.56 (–9.54 to 2.43)	–0.290	.24
Muscle locking, overall	43	40.0 (33.1 to 46.7)	53.8 (46.4 to 61.1)	–13.7 (–20.4 to –7.03)	–0.888	<.001
Pain, overall	32	39.9 (30.6 to 49.0)	48.2 (39.2 to 57.1)	–8.32 (–13.8 to –2.87)	–0.782	.004
Fatigue, overall	35	48.4 (40.9 to 56.6)	58.3 (50.6 to 66.0)	–9.96 (–17.0 to –2.93)	–0.678	.007
Activity, overall	51	34.2 (26.7 to 43.0)	47.1 (40.1 to 55.5)	–12.9 (–18.3 to –7.43)	–0.950	<.001
Independence, overall	51	17.8 (12.3 to 23.3)	22.5 (17.2 to 28.1)	–4.74 (–8.14 to –1.35)	–0.561	.007
Social relations, overall	51	18.9 (13.5 to 24.5)	25.9 (18.0 to 35.2)	–7.02 (–13.4 to –0.671)	–0.440	.03
Emotions, overall	51	27.7 (22.0 to 34.4)	33.8 (27.1 to 41.5)	–6.13 (–10.1 to –2.15)	–0.619	.003
Body image, overall	51	24.2 (17.3 to 31.0)	29.4 (22.0 to 36.5)	–5.27 (–10.4 to –0.105)	–0.408	.05
QOL, overall	51	14.0 (11.6 to 16.5)	16.7 (14.0 to 19.4)	–2.69 (–4.07 to –1.30)	–0.780	<.001
Perceived treatment effect, overall	51	36.6 (27.1 to 45.8)	21.7 (12.7 to 31.1)	14.9 (7.43 to 22.3)	0.797	<.001
Expected treatment effect, overall	51	36.1 (26.9 to 47.0)	23.1 (14.5 to 33.6)	13.0 (4.18 to 21.8)	0.585	.005
Clinical assessment, overall, seconds						
Eye closure[d]	57	0.161 (0.0704 to 0.314)	0.474 (0.261 to 0.871)	–0.313 (–0.602 to –0.149)	–0.888	<.001
Handgrip[d]	57	0.164 (0.0858 to 0.294)	0.494 (0.281 to 0.872)	–0.330 (–0.633 to –0.142)	–0.748	<.001
QMA handgrip[e]	54	0.321 (0.274 to 0.370)	0.429 (0.365 to 0.517)	–0.109 (–0.177 to –0.0560)	–0.518	<.001

Abbreviations: INQOL, Individualized Neuromuscular Quality of Life; QMA, quantitative myotonia assessment; QOL, quality of life; RADM, right abductor digiti minimi; RTA, right tibialis anterior; SF-36, 36-Item Short-Form Health Survey.

[a] The CIs for the predicted treatment group means are boot strap CIs, which reflect precision of estimates without exploiting the correlated nature of the data unlike the treatment effect CIs. All treatment effect estimates and CIs are extracted from mexiletine treatment variable of the fitted mixed model. The effect size is the treatment effect estimate divided by within-participant SD. *P* value indicates significance level of the Wald test associated with mexiletine effect from the additive model, when no carryover effect was detected. When a carryover effect was detected, the significance level associated with the additive portion of the mexiletine effect (labeled period 1) followed in the next row by the level associated with the interaction of mexiletine and period 2 (labeled period 2). The exceptions are 2 needle electromyographic tests in which the Wilcoxon test was substituted because the outcome is not a continuous variable and therefore normality of the residuals is not satisfied.

[b] Primary outcome: 52 participants contributed to both periods while 5 only contributed to period 1.

[c] Only participants that experienced this symptom were included.

[d] Treatment-specific group mean is a geometric-like mean estimate using the log(t+0.1) "normalizing" transformation. Treatment effect estimate is the difference between the treatment-specific group means.

[e] Treatment-specific group mean is a geometric mean estimate. Treatment effect estimate is the difference between the treatment-specific group means.

Baseline Data

We studied 33 men and 26 women, with mean age of 42.9 years (range, 16-68 years). Participants were predominantly white (57/59 [96.6%]) and non-Hispanic (46/59 [78.0%]). Thirty-four participants had chloride channel mutations, 21 had sodium channel mutations, and 4 had no mutation identified. Seventeen participants were taking medications for myotonia before the start of the study, including 13 (22.0%) taking mexiletine (TABLE 1). Randomization between groups was balanced, with the exception of more men in the placebo followed by mexiletine group.

Figure 2. Weekly Stiffness Severity Scores by Treatment Sequence

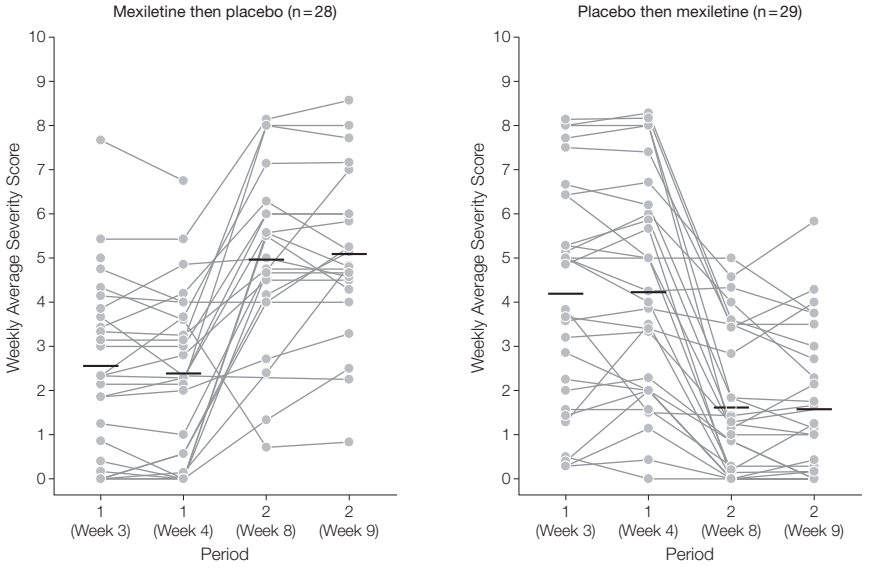
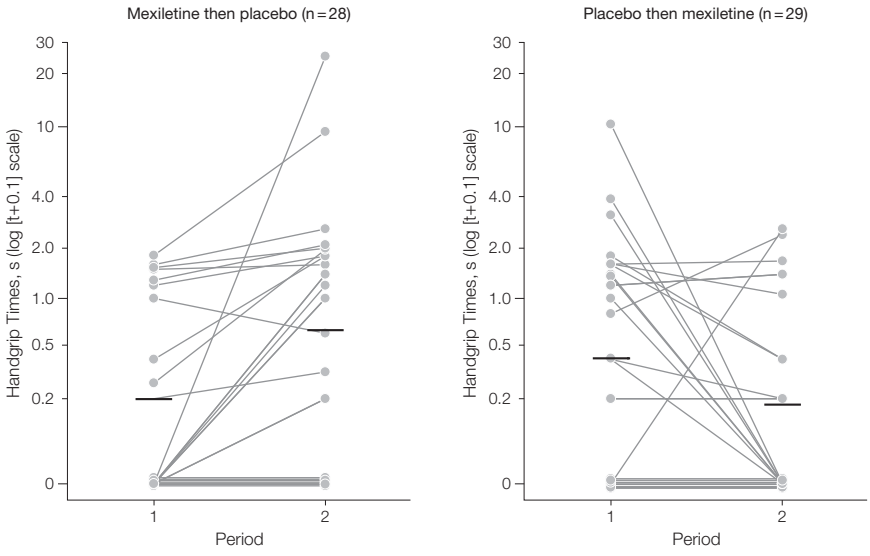


Figure 3. Clinical Evaluation of Handgrip Myotonia Times by Treatment Sequence



Actual times displayed on log(t+0.1) scale to correspond with the normalizing transformation used for analysis. Zero times for some participants required the translation value of 0.1 to be added, then scaling with the natural log function.

Numbers Analyzed and Drug Levels

Data from 57 participants who made telephone calls to the IVR diary in weeks 3 to 4 of period 1 or 2 were included in the analysis (Figure 1). Adherence for the primary end point, stiffness on the IVR diary, was achieved in 74.3% of possible telephone calls (78.6% in period 1 and 70.0% in period 2).

Pill adherence was similar between treatments (means for the ratio of the number of pills "taken" to the number of pills distributed were 90.2% for mexiletine vs 92.7% for placebo for period 1 and 93.0% for mexiletine vs 92.7% for placebo for period 2). Mexiletine levels at baseline, the end of washout, and the end of both placebo groups were not detectible. The mean (SD) mexiletine level at the end of mexiletine treatment periods was 0.54 (0.35) µg/mL (reference antiarrhythmic therapeutic range for 600-1200 mg/d, 0.5-2.0 µg/mL).

Outcomes and Estimations

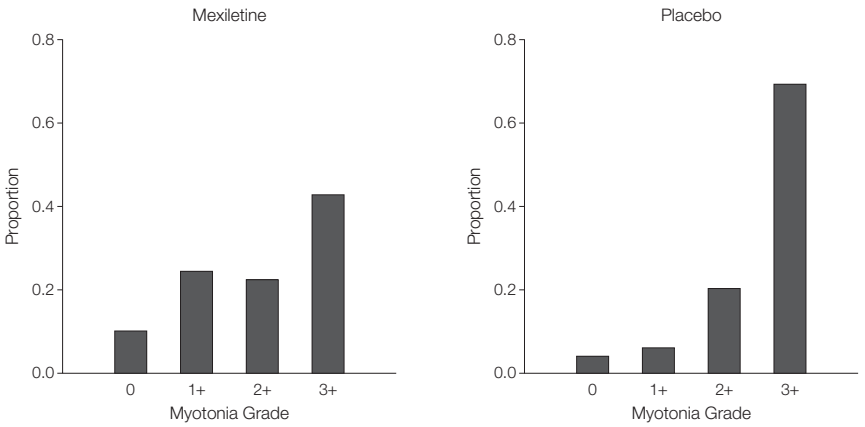
Mexiletine was associated with significantly improved stiffness as reported on the IVR diary in both treatment periods. As explained in the Methods section, we estimated the treatment effect for each period separately. For period 1, the treatment effect was 2.53 for mexiletine vs 4.21 for placebo (difference, –1.68; 95% CI, –2.66 to –0.706; $P<.001$); and for period 2, 1.60 for mexiletine vs 5.27 for placebo (difference, –3.68; 95% CI, –3.85 to –0.139; $P=.04$) (TABLE 2 and FIGURE 2).

There were significant improvements with mexiletine in most other outcomes in the study, including patient-reported outcomes, QOL scales, and quantitative measures of myotonia (Table 2). Mexiletine improved the SF-36 physical composite score (mexiletine, 44.8 vs placebo, 39.2; difference, 5.58; 95% CI, 3.44-7.72; $P<.001$) and INQOL summary QOL score (mexiletine, 14.0 vs placebo, 16.7; dif-

ference, –2.69; 95% CI, –4.07 to –1.30; $P < .001$).

Mexiletine improved myotonia as measured on clinical examination by overall handgrip times in seconds (mexiletine, 0.164 seconds vs placebo, 0.494 seconds; difference, –0.330; 95% CI, –0.633 to –0.142; $P < .001$) (FIGURE 3) and overall QMA handgrip 90% to 5% relaxation times (mexiletine, 0.321 seconds vs placebo, 0.429 seconds; difference, –0.109; 95% CI, –0.177 to –0.0560; $P < .001$). Electrophysiological measures of myotonia showed a mixed response. Mexiletine significantly improved the severity of graded myotonia on electromyography (right abductor digiti minimi: difference, –0.568; 95% CI, –0.812 to –0.325; $P < .001$) (FIGURE 4). There was no statistically significant association with mexiletine and electrophysiological exercise testing.

Figure 4. Graded Myotonia on Electromyography for Right Abductor Digiti Minimi (n=56) in Placebo and Mexiletine Treatment Groups



Myotonia grading: 0=no myotonia; 1+=myotonic discharges at least 500 ms and elicited in 3 areas of the muscle outside of the endplate zone; 2+=myotonic discharge in more than ½ of needle locations; and 3+=myotonic discharges with each needle movement in all examined areas.[19]

Ancillary Analyses

The reduction in the severity of stiffness score was more pronounced for participants with chloride mutations than sodium mutations in period 2 (chloride, –4.18; 95% CI, –5.25 to –3.12; vs sodium, –2.67; 95% CI, –3.84 to –1.51; $P=.003$) (eTable), but showed to be the reverse in period 1 (chloride, –1.67; 95% CI, –2.73 to –0.614; vs sodium, –2.11; 95% CI, –3.28 to –0.933). In addition, the decrease in the clinical quantitative myotonia assessment handgrip times was greater for participants with chloride mutations than sodium mutations (chloride, –1.24 seconds; 95% CI, –1.77 to –0.711 seconds; vs sodium, –0.355 seconds; 95% CI, –1.03 to 0.316 seconds; $P=.04$).

Safety

There was 1 serious adverse event determined to be not study related (narcotic withdrawal). The most common adverse event was gastrointestinal in 9 participants in the mexiletine group and in 1 participant in the placebo group (TABLE 3). There were 2 reported cardiac adverse events both found incidentally on electrocardiogram at the end of week 4 (1 patient had bradycardia in the mexiletine group that resolved on follow-up electrocardiogram and 1 patient had premature ventricular complexes in the placebo group). Neither necessitated stopping the study.

Survey

A survey performed after the completion of each study period asked participants to guess their treatment allocation during the preceding period. The number of participants who guessed correctly was 18 (64%) in the mexiletine group and 20 (69%) in the placebo group during period 1, and 23 (79%) in the mexiletine group and 20 (80%) in the placebo group during period 2.

Table 3. Adverse Events of the Mexiletine and Placebo Treatment Groups

Adverse Event Category	Mexiletine Treatment	Placebo Treatment
Cardiac	1	1
Constitutional	3	0
Dermatologic/skin	1	2
Gastrointestinal	9	1
Infection	1	3
Lymphatics	0	1
Musculoskeletal/soft tissue	0	2
Neurologic	5	1
Pain	4	0
Total	**24**	**11**

COMMENT

Our study provides preliminary evidence of the effectiveness of mexiletine for symptoms and signs of myotonia in NDMs. There was a significant increase in IVR diary treatment effect for stiffness in period 2 compared with period 1. This so called "carryover" effect is contrary to the usual definition of "the persistence of a treatment applied in one period in a subsequent period of treatment."[27] There was no evidence for a lingering effect of mexiletine into period 2. Washout of mexiletine was effective (drug levels zero or not detectible after washout).

There was no evidence of an unbalanced effect based on group assignment. The aggregate within participant difference between mexiletine and placebo groups was similar whether participants received mexiletine followed up by placebo (–2.55) or placebo followed up by mexiletine (–2.62). It is possible that unintentional unblinding of participants was associated with this increase.

The cause-effect mechanism can be explained in 1 of 2 ways: (1) unintentional unblinding was due to a true treatment effect, which suggests that ad-

ditional benefit detected in period 2 is attributable to mexiletine; or (2) the adverse effects of mexiletine (or the absence of adverse effects for those participants receiving placebo) in period 2 lead to exaggerating the score to a lower (or higher) value. It is not possible to tease out from the data which explanation is correct. The effect for period 1 confirms its significance ($P<.001$) and represents the lower bound of the treatment effect in our trial. The fairest interpretation we can propose is that the treatment effect lies somewhere between the estimates from period 1 (–1.68) and period 2 (–3.68).

The clinical significance of the improvement in stiffness score on the IVR diary is supported by the broad improvement in clinical, quantitative, and electrophysiological measures of myotonia. Although patient-reported outcomes might be susceptible to exaggeration by participants who had guessed their treatment assignment, quantitative measures are not (mexiletine decreased myotonia on both quantitative handgrip testing and electromyography). Overall, most effect sizes were more than 0.5, which in the literature corresponds with moderate responsiveness, and more than 0.8, which corresponds with large responsiveness, for many outcomes (stiffness, weakness, and pain on the IVR diary, SF-36 physical composite score, clinical eye closure myotonia, and electrophysiological myotonia grades) (Table 2).[28-31] Many studies have suggested that statistically an effect size of 0.5 corresponds well to minimally clinically important differences in health-related QOL instruments.[32-35]

Mexiletine was well tolerated in our study. Gastrointestinal discomfort was the most common adverse event, and there were no serious study-related adverse events.

Limitations to our study include the short duration of treatment, limited power for detecting adverse events, and the inclusion of participants with both chloride and sodium channel mutations in a single group to obtain necessary study power. Although there was an indication mexiletine resulted in greater improvement in stiffness score for participants with chloride channel mutations vs sodium channel mutations in period 2, the opposite was true in period 1. The clinical implications for this are not clear. Both groups appear to have improved with mexiletine, and the study is not powered to determine relative effectiveness by mutation.

In conclusion, our study provides preliminary evidence of the effectiveness of mexiletine for patients with myotonia. The RDCRN provided common data elements and the centralized infrastructure necessary for such a broad international collaboration, and serves as a model for future research of rare diseases.

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