Mexiletine Improves Symptoms and Signs of Myotonia in Non-dystrophic Myotonia

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ABSTRACT (245 words / 250 word max)

Background: The non-dystrophic myotonias (NDM) result from mutations of muscle ion channels. Patients experience delayed muscle relaxation following contraction, functionally limiting stiffness and pain. Case studies and a single-blind trial suggest mexiletine reduces myotonia in NDM. Due to NDM's rarity larger studies of safety and efficacy have not been possible. The centralized infrastructure of the Rare Disease Clinical Research Network provided a unique opportunity to conduct a phase II multi-center trial in NDM.

Methods: We conducted a multi-center randomized, double-blind, placebo-controlled two-period cross-over trial of mexiletine 200 mg three times daily in 59 NDM patients. Each period was 4 weeks in duration with one-week washout. Patient-reported stiffness recorded on an interactive voice response diary (IVR) was the primary endpoint. Secondary endpoints included changes in pain, weakness, and tiredness on IVR, clinical myotonia assessment, quantitative grip myotonia, INQoL, SF-36, electrophysiological short and long exercise testing, and needle EMG.

Results: Mexiletine significantly improved patient-reported stiffness (-2.69, $p<0.0001$), as well as all other symptoms on the IVR. In addition, a similar improvement was seen on the physical and mental components of the SF36 and INQol. Improvements in patient-reported symptoms corresponded with significant reductions in quantitative measures of myotonia. The most common adverse effect was gastrointestinal (9/59), and cardiac effects were rare. One serious adverse event was determined to be not study related.

Conclusion: Mexiletine at a dose of 200 mg three times daily was safe and effective therapy for the most common symptoms of myotonia in NDM patients.

INTRODUCTION

The non-dystrophic myotonias (NDM) are rare disorders caused by mutations in muscle chloride and sodium channels with the common clinical feature of myotonia without muscle wasting[1]. Although not life-threatening, myotonia causes lifelong morbidity: muscle stiffness, pain, fatigue and weakness. Data on treatment of NDM is largely anecdotal: case series and a single blind controlled trial of quinine[2], procainamide[2,3], phenytoin[3], tocainide[4], and mexiletine[5,6]. A 2006 Cochrane review concluded there was not sufficient data to consider any treatment safe and effective for myotonia[7].

Mexiletine is a class 1B antiarrhythmic medication with a high affinity for muscle sodium channels. *In vitro* data and animal models suggest mexiletine corrects the delay in inactivation caused by common NDM sodium channel mutations[8-10], and significantly improved the righting reflex in the ADR mouse, a model for chloride channel NDM[11]. A recent randomized controlled crossover study showed mexiletine to be safe and effective for reducing myotonia in patients with myotonic dystrophy[12].

The major impediment to randomized controlled trials in NDM is its rarity, with an estimated prevalence of 1:100,000[13]. The Rare Disease Clinical Research Network (RDCRN) is an n NIH-funded initiative designed to provide centralized data storage and analysis for investigations into rare diseases. A network Consortium for Neurological Investigations into Neurological Channelopathies (CINCH) includes 7 national and international sites with expertise in NDM. In a prior natural history study we introduced an interactive voice response(IVR) diary of patient symptoms and found stiffness was the most common and severe symptom reported in NDM

regardless of mutation subtype[14]. Here we report a randomized, placebo-controlled cross-over study of the safety and effectiveness of mexiletine in NDM using patient reported stiffness on the IVR as the primary outcome.

METHODS

Trial Design:

We conducted a multi-center randomized, double-blind, placebo-controlled cross-over trial at 7 centers in 4 countries. The treatment periods were 4 weeks in duration separated by a 1 week washout period. The trial was approved by institutional review boards and written and informed consent was obtained from all participants. The National Institutes of Health established a Data Safety Monitoring Board (DSMB) which met every 6 months to monitor progress of the study and adverse events.

Participants:

Eligible participants were at least 16 years of age, had clinical symptoms or signs of NDM, and myotonic potentials on electromyography. Participants were either enrolled in the CINCH NDM: Genotype-Phenotype Correlation and Natural History Study, or a new patient with genetically confirmed NDM, or with clinical features of NDM in whom the mutation has not been identified, but myotonic dystrophy testing was negative. Patients taking medications reported to cause myotonia were required to be on a stable dose for 30 days prior to enrolment. Patients currently taking symptomatic medications for myotonia were required to discontinue medications for a wash-out period equal to seven times the half-life of elimination of the drug prior to enrollment.

Particpants were ineligible if they were unable or unwilling to provide informed consent, had other neurological conditions that might affect the assessment of the study measurements, or

had genetic confirmed DM1 or DM2. Women who were pregnant or lactating were ineligible. Patients were excluded if they had contraindications to taking mexiletine (cardiac conduction defect, renal or hepatic disease, or heart failure), or were taking other antiarrhythmic medications contraindicated for use with mexiletine.

The study was performed between April 2008 to March 2011 at the following RDCRN/CINCH sites: University of Kansas Medical Center, University of Rochester Medical Center, Brigham and Women's Hospital, University of Texas Southwestern, London Health Sciences Center, Institute of Neurology, and the University of Milan.

Most participants were recruited from the CINCH NDM natural history study. Participants were also recruited by information posted on the RDCRN website, the websites of the Periodic Paralysis Association and the Muscular Dystrophy Association, and their publications.

Interventions:

Participants were randomized to mexiletine 200 mg capsules orally three times a day (TID) or placebo 200 mg capsules TID for 4 weeks. After a 1 week wash-out period, they were placed on the opposite study regime for 4 weeks.

Mexiletine was purchased from TEVA Pharmaceutical. The mexiletine and placebo were encapsulated at the University of Iowa Research Pharmacy. A Qualified Person from Brecon inspected TEVA and the University of Iowa Research Pharmacy for the purpose of the European Directive.

Outcomes:

For the Interactive Voice Response Diary (IVR) calls were made daily for the entire 9 week study. All other outcomes measurements were performed at baseline, the end of each treatment period, and the end of washout prior to the start of period two.

Primary Outcome Measure: The primary endpoint was defined as the severity level of stiffness (whole numbers from 1 to 9) during the third and fourth week of each treatment period reported daily by the participants via the IVR. Details of this device and preliminary data have been published[14]. In summary, using a call-in procedure, patients reported symptom frequency and severity on a 1-9 scale, one being minimal, 9 being the worst ever experienced (Supplementary Figure 1). All responses were automatically stored on a central database.

Secondary Outcome Measures

1) Participant-assessed pain, weakness, and tiredness as measured by the IVR from daily calls made over the last two weeks of each period. 2) A clinical myotonia beside assessment was performed: participants were asked to squeeze their eyes closed for 5 seconds then rapidly open them; or make a tight fist for 5 seconds then rapidly open. Five trials of each maneuver were performed at each visit and the time measured on 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 90% to 5% relaxation times were determined using automated analysis software[15,16]. 4) Measurement of compound muscle action potential (CMAP) after short and long exercise was performed as previously described[1,17]. 5) Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti minimi and right

tibialis anterior[18]. 6) Patients filled out the SF-36 and the Individualized Quality of Life questionnaire for neuromuscular disorders.[19]

Sample Size:

The sample size goal was set to 54 subjects with available primary endpoint measurements for both treatment periods. This sample size provided at least 93% power to detect an effect size of one-quarter of a standard deviation (within subject) in the primary endpoint with a 2-sided hypothesis test and an alpha level to 0.05. This determination included the assumption that there were 5 measurements for each of the four weeks to be included in the analysis. The variation in power was due to varying the degree of between-subject standard deviation; larger standard deviations lowered the power since the effect in the active treatment period for low severity scores cannot be less than 0.

Randomization:

Randomization occurred at the Data Management Coordinating Center at the University of South Florida in Tampa Florida. Randomization was balanced providing an equal chance of receiving mexiletine followed by placebo or placebo followed by mexiletine.

Participants, physicians, and evaluators were blinded to medication assignment. Only the NIH-sponsored DSMB who met every 6 months had access to treatment assignment.

Statistical Analysis:

The method of analysis used included both linear mixed-effects model (random effect for subject) and paired t-test[20,21]. The paired t-test results are provided for the main treatment comparisons although the mixed model results were very similar. The paired t-test analysis was limited to subjects who provided outcome measurements for both treatment periods. The one exception to this approach was for the two electrographic myotonia assessments (see below). The mixed model allowed for covariate adjustment, including period, gender and age as well as a linear structure of time for the endpoints, QMA hand grip, short exercise and prolonged exercise. The mixed model was also used to conduct a homogeneity test of treatment effect across subgroups of mutation class. Normality assumptions were applied in computing 95% confidence intervals of the treatment effect differences, standard errors and other descriptive statistics.

A departure from normality was detected using QQ plots of the daily self-reported symptom severity scores. By substituting the average severity score per week this departure was eliminated.

For the electrographic myotonia assessment the score was converted to a numeric value as follows: absent was set to 0, 1+ was set to1, 2+ was set to 2, and 3+ was set to 3. The endpoint was the sum of the numerical scores of the two muscles. A Paired Wilcoxon test was used to test the hypothesis that the medians of the two samples are equal[22].

Since this trial identified a primary endpoint, all other p-values presented were for secondary endpoints and are not adjusted for multiple testing. All p-values are two-sided.

RESULTS

Participant Flow:

Eligible subjects were recruited between December 2008 and January 2011. Of 62 participants recruited, 3 were ineligible: 1 had a prolonged QT at screening visit, 1 had an elevated transaminase, and 1 had no clinical myotonia on examination. Fifty-nine participants were randomized to receive study medication or placebo. There were 4 dropouts: 1 secondary to migraine headaches, 1 secondary to gastric discomfort, and 2 for noncompliance (Figure 1).

Baseline Data:

We studied 33 men and 26 women, mean age 42 years (16 to 68 years). Participants were predominately white (97%) and non-Hispanic (78%). Thirty-two participants had chloride channel mutations, 21 had sodium channel mutations, and 6 had no mutation identified (see Table 1).

Numbers Analyzed:

Fifty-two participants completing the study were included in analysis. Three participants were excluded from the primary analysis due to failure to make at least one call per week to the IVR system. Expected compliance for the primary endpoint, stiffness on the IVR, was 10 of 14 possible calls per period (71.4%). Overall actual compliance was 74.3% of possible calls (78.6% in period 1, and 70% in period 2).

Outcomes and Estimations:

Mexiletine significantly improved stiffness, the primary outcome, on the IVR during weeks 3-4 and weeks 8-9 (-2.69, $p<0.001$, Table 2, Figure 2A).

There were significant improvements with mexiletine in almost all other outcomes in the study, in patient-reported outcomes, quality of life scales, and quantitative measures of myotonia (Table 2). Mexiletine improved all symptoms reported on the IVR. Almost all categories measured on the SF-36 showed significant improvement, most notably the composite physical and mental health scores (Figure 2B). Mexiletine improved almost all categories on the INQoL, including the overall QOL score, muscle locking and perceived treatment effect (Figure 2C).

Both eyelid and handgrip myotonia measured on clinical examination improved (Figure 2D). A quantitative, automated measure of handgrip myotonia showed decreased handgrip 90% to 5% relaxation times. Electrophysiological measures of myotonia also improved. The post exercise decrement in compound muscle action potential characteristic for different mutation types in NDM was decreased on short exercise testing. The severity of graded myotonia on electromyography was reduced in the abductor digiti minimi and tibialis anterior (Figure 2E). As might be expected there was no treatment effect on the long exercise test, which is typically normal to only mildly abnormal for chloride channel subjects, who make up the majority of the NDM population in this study[17,23].

Ancillary Analyses:

In order to shed light on whether the treatment effect of mexiletine seen in this study applies equally to NDM patients with chloride or sodium channel mutations we tested the post-hoc

hypothesis that there is no difference between groups using homogeneity testing (supplementary Table 1). When comparing the effects of mexiletine there is no interaction based on underlying chloride or sodium channel mutation for the primary endpoint, stiffness on the IVR (p=0.020), for the other symptoms on the IVR, the SF-36 physical and mental composite scores, the INQoL QOL score and clinical handgrip myotonia evaluation. For the clinical eyelid myotonia evaluation sodium subjects have a greater treatment effect versus chloride channel subjects (p=0.04). This would be consistent with the observation that eyelid myotonia is more common in sodium channel NDM patients[23,24].

Safety:

There was one serious adverse events recorded in this study. That person was admitted to the hospital for narcotic withdrawal, and it was determined to not be study related. The most common adverse event was gastrointestinal (9/59). Most of the symptoms were relieved with over the counter medication or a reduction of mexiletine to twice daily dosing. One patient did not continue with the second phase of the study due to gastric discomfort. Other adverse events were cardiac (increase in PVC's, short term bradycardia), constitutional (insomnia), dermatology/skin (rashes), infection (sinus), neurologic (tremors), and pain (headache) (Table 3). The incidence of adverse cardiac events was not different between mexiletine and placebo.

DISCUSSION

This study provides class 1 evidence that mexiletine at 200 mg three times daily significantly improved stiffness, pain, weakness and tiredness in subjects with NDM. In addition mexiletine also significantly improved quality of life and quantitative measures of myotonia. Side effects of mexiletine were mild, primarily gastrointestinal discomfort and there were no serious study-related adverse events.

Prior studies with mexiletine in NDM have been limited to case studies and a single-blind trial. In 1994 Jackson and Barohn demonstrated an improvement on the short exercise test following mexiletine in a patient with paramyotonia congenita and a missense mutation in the SCN4A gene, the first such report in a patient with a molecularly-defined NDM subtype[5]. A single blind trial compared placebo to phenytoin in a cross over design, followed by randomization to receive mexiletine, tocainide, or disopyramide[6]. The study included both myotonic dystrophy and NDM patients, and there was no wash-out period between arms. The researchers concluded that mexiletine and tocainide were the most potent anti-myotonic agents. Despite the beneficial effects of tocainide on myotonia seen in this study and another open label trial[6,25], the tendency of tocainide to cause bone marrow suppression precludes its acceptability for the long-term treatment of myotonia[26,27]. More recently investigators at the University of Rochester showed mexiletine at a dose of 200 mg three times daily was safe and effective therapy for myotonia (reducing 90% to 5% handgrip relaxation time) in a randomized, placebo-controlled, cross over trial in patients with myotonic dystrophy[12].

NDM is due to mutations in chloride and sodium channels. Mutations in chloride channels result in a greatly diminished sarcolemmal chloride conductance[28]. In the absence of this resting chloride conductance, elevations of the potassium concentration in the t-tubular lumen during electrical activity cause a depolarization of the sarcolemmal membrane and, consequently, muscle hyperexcitability [29]. Mutations in sodium channels result in a delay in fast or slow inactivation gating, or a shift in sodium channel activation to more hyperpolarized potentials, leading to hyperexcitable muscle fibers[30-33]. We propose that mexiletine, by its high affinity antagonism of muscle sodium channels reduces overall muscle fiber excitability regardless of underlying mutation type[9,10].

This is the first large clinical trial conducted using the NIH-sponsored Rare Disease Clinical Research Network (RDCRN). It is extremely challenging to complete a randomized, placebo-controlled trial in NDM because of the rarity of this disorder. This study would not have been possible without the prior experience of the CINCH NDM natural history study, and the RDCRN infrastructure. This broad collaboration—with common data elements and centralized data management and analysis—is a prototype for NIH-sponsored rare disease research.

Increasingly funding agencies including the NIH and MDA have emphasized the critical importance of patient-relevant outcome measures for trials in muscular dystrophy[34], and the FDA has emphasized importance of developing outcome measures that are clinically meaningful and based on the patient's perspective.[35] We elected to use a patient-reported measure of stiffness on the IVR as our primary outcome instead of a quantitative measure of myotonia because we believe that for symptomatic treatment change in patient-reported

symptoms is a more meaningful outcome. Mexiletine at a dose of 200 mg three times daily significantly improved patient-reported symptoms related to myotonia in NDM. This patient-reported benefit is supported by improvements in quality of life and quantitative measures of myotonia.

Mexiletine is a generic medication rarely used for its original indication of cardiac arrhythmias that is currently on the FDA drug shortage list[36]. We feel this study, in combination with the recent study in myotonic dystrophy, provides convincing evidence of the effectiveness of mexiletine for myotonia. We hope these studies provide a strong incentive to drug manufacturers to keep supplying this valuable antimyotonic agent.

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APPENDIX

Individual Study Site Participants:

University of Kansas Medical Center: Investigators: Richard J. Barohn, MD (Principle Investigator, Steering Committee, Manuscript Preparation, Yunxia Wang, MD (Co-Principle Investigator, Steering Committee, Manuscript Preparation), Jeffrey Statland, MD (Steering Committee, Manuscript Preparation), Mazen Dimachkie, MD; Project Manager/Study Coordinator/Clinical Evaluator: Laura Herbelin CCRP (Steering Committee, Manuscript Preparation); Central Cardiologist: Rhea Pimental, MD

University of Texas Southwestern Medical Center: Investigators: Jaya Trivedi, MD (Manuscript Preparation); Study Coordinator: Nina Gorham, CCRP, Clinical Evaluator: Rhonda McLin, PTA, Vivian Gonzales)

Brigham and Women's Hospital: Investigators: Mohammad Kian Salajegheh, MD (Steering Committee, Manuscript Preparation), Anthony A. Amato, MD; Study Coordinator: Kristen Roe BS; Clinical Evaluator: Samatha Chused, MSPT, Essa Kayd, RT.

London Health Science Center (London Ontario Canada): Investigators: Shannon Venance, MD (Steering Committee, Manuscript Preparation), Angelica Hahn, MD; Study Coordinators/Clinical Evaluators: Wilma Koopman, Jennifer Verheyden, Ashley Ten Haaf, Christine Piechowicz.

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Institute of Neurology (London, England): Investigators: Michael Hanna, MD (Steering Committee, Manuscript Preparation), Dipa L. Raja Rayan, MRCP, Emma Matthews, MRCP; Study Coordinators/Clinical Evaluator: Gisela Barreto, Veronica Tan, James Burge, Elizabeth Dewar, Daleen Lopez-Begum; Genetic testing: Richa Sud, Andrea Haworth, Samuel McCall.

University of Milan (Milan, Italy): Investigators: Valeria Sansone, MD (Manuscript Preparation), Giovanni Meola, MD, Alice Zanzoni, MD, and Matteo Ciocca, MD.

University of South Florida (DMCC): Statistician: Brian Bundy, PhD (Steering Committee, Data Analysis, Manuscript Preparation); Jeffrey Krischer, PhD, Holly Ruhlig, Joseph Gomes, Rachel Richesson, Renee Leduc, Jennifer Pilger.

DSMB Members

John W. Day, MD; Ph.D. (Standford School of Medicine, Stanford, CA), Robert T. Leshner, MD (UC San Diego, San Diego, CA), Todd A. Mackenzie, Ph.D. (Dartmouth Hitchcock Medical Center, Hanover, NH), and Kathryn Wagner, MD, Ph.D. (The Johns Hopkins School of Medicine, Baltimore, MD)

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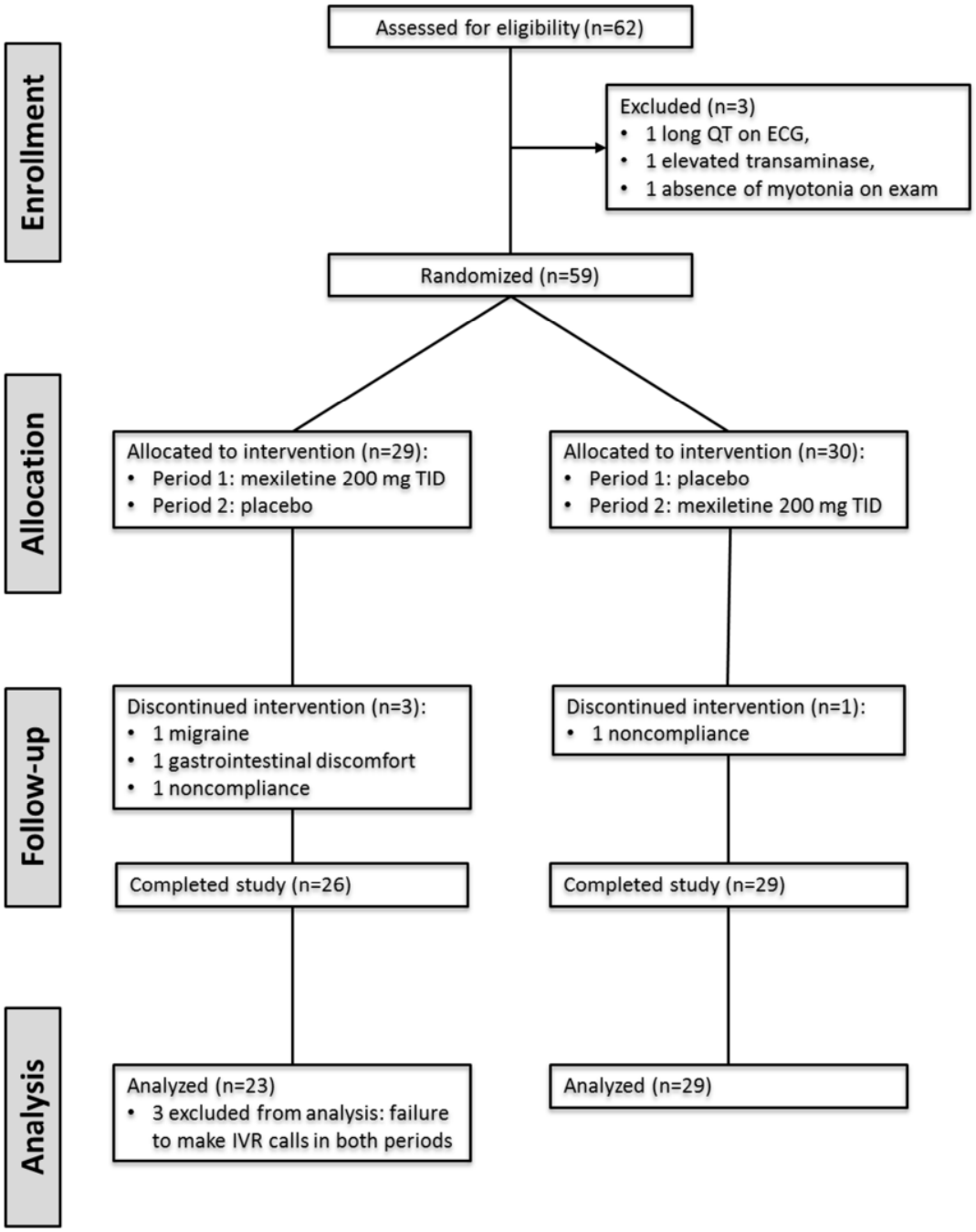
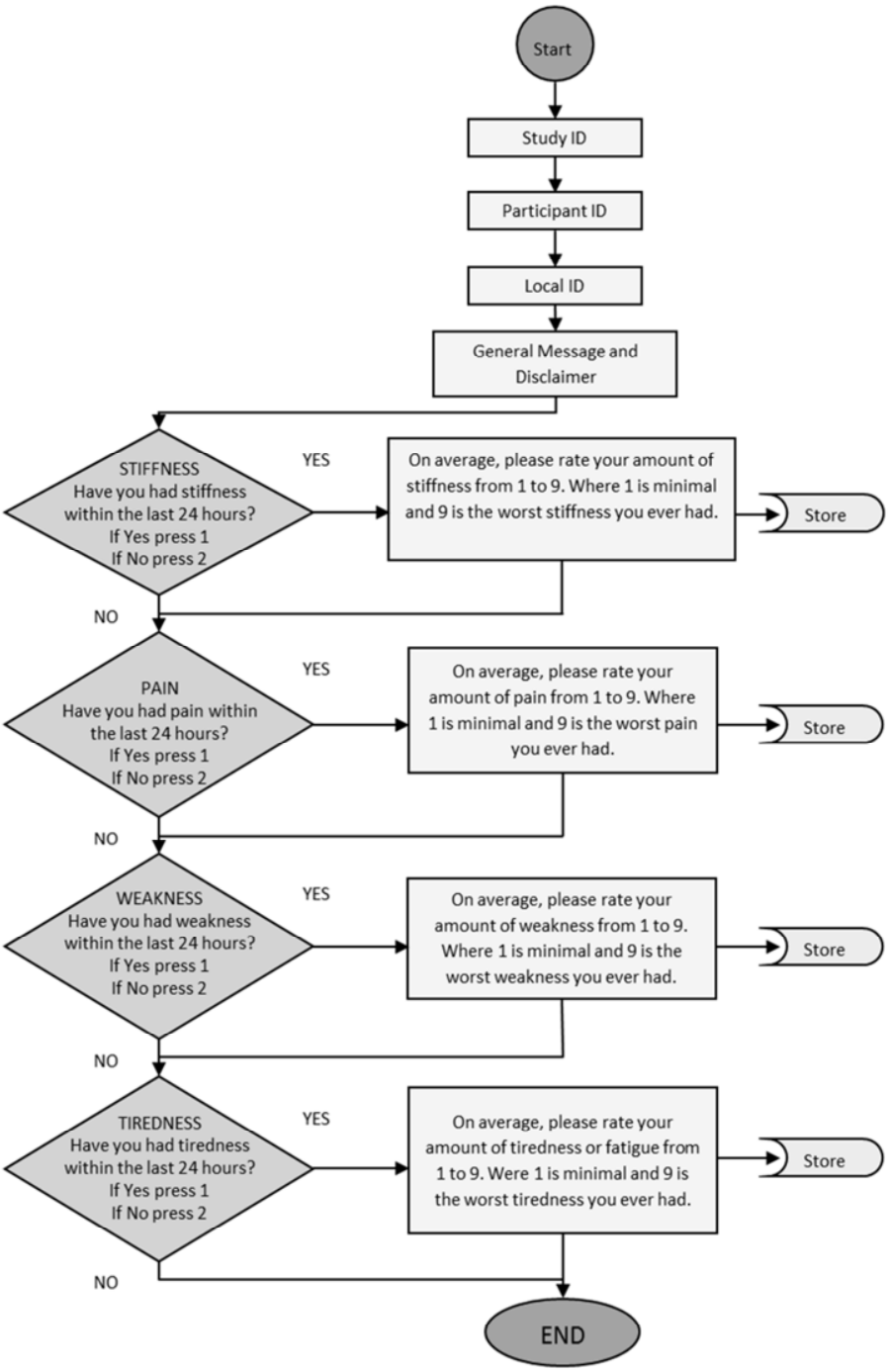


Figure 1. Study design and disposition of patients



Supplementary Figure 1. IVR Flow Diagram

Table 1. Screening Characteristics

Age Mean/Range (Years)	42/16-68
Gender Male/Female (%)	33 (55.9%) / 26 (44.1%)
Race White (%) Black (%) Unknown (%)	 57 (96.6%) 1 (1.7%) 1 (1.7%)
Ethnicity Hispanic (%) Non-Hispanic (%)	 13 (22.0%) 46 (78.0%)
Na^+ Channel Mutation	21
Cl^- Channel Mutation	32
No Mutation Identified	6

Table 2: Mean Difference and Responsiveness Statistics

Endpoint	No.	Treatment Effect Estimate*	95% Confidence Interval	p-value†
IVR—Stiffness‡	52	-2.69	-3.26, -2.12	< 0.001
IVR—Pain§	47	-1.48	-2.03, -0.937	< 0.001
IVR—Weakness§	44	-1.16	-1.77, -0.544	< 0.001
IVR—Tiredness§	48	-0.900	-1.49, -0.309	0.004
Short Exercise (% decrement)	51	5.50	1.05, 9.94	0.016
Prolonged Exercise (% decrement)	51	2.55	-1.95, 7.04	0.26
Needle EMG RADM	49	-0.571	-0.820, -0.323	< 0.001#
Needle EMG RTA	49	-0.490	-0.702, -0.277	< 0.001#
SF36 – Physical Function	52	5.18	2.94, 7.42	< 0.001
SF36 – Role Physical	52	7.16	4.45, 9.87	< 0.001
SF36 – Bodily Pain	52	7.60	4.85, 10.3	< 0.001
SF36 – General Health	51	0.925	-0.713, 2.56	0.26
SF36 – Vitality	52	6.66	3.34, 9.98	< 0.001
SF36 – Social Function	52	5.24	2.62, 7.86	< 0.001

Endpoint	No.	Treatment Effect Estimate*	95% Confidence Interval	p-value†
SF36 – Role Emotional	52	5.64	2.68, 8.61	< 0.001
SF36 – Mental Health	52	4.26	1.74, 6.78	0.001
SF36 – Physical Composite	51	5.54	3.35, 7.74	<0.001
SF36 – Mental Composite	51	4.78	2.18, 7.38	< 0.001
INQoL - weakness	35	3.91	-9.98, 2.16	0.19
INQoL – muscle locking	43	-13.8	-20.6, -7.02	< 0.001
INQoL - pain	32	-8.72	-14.2, -3.21	0.003
INQoL - fatigue	35	-10.4	-17.5, -3.27	0.006
INQoL - activity	51	-12.7	-18.2, -7.19	< 0.001
INQoL - independence	51	-4.52	-7.91, -1.13	0.010
INQoL – social relations	51	-7.03	-13.5, -0.513	0.04
INQoL - emotions	51	-6.10	-10.2, -2.01	0.004
INQoL – body image	51	-5.28	-10.5, -0.0980	0.05
INQoL - QOL	51	-2.69	-4.07, -1.31	< 0.001
INQoL – perceived rx effect	51	15.2	7.70, 22.7	< 0.001

Endpoint	No.	Treatment Effect Estimate*	95% Confidence Interval	p-value†
INQoL – expected rx effect	51	13.6	4.66, 22.5	0.004
Clinical assessment - eye closure (seconds)	51	-1.04	-1.86, -0.214	0.02
Clinical assessment – hand grip (seconds)	51	-1.27	-2.37, -0.174	0.02
QMA Hang Grip (seconds)	43	-0.210	-0.335, -0.0852	0.002

* All treatment effects are the difference between mexiletine minus placebo

† Simple paired t-test (no covariate adjustment)

‡ Primary outcome: 3 subjects excluded because they did not make IVR stiffness reports in both periods

§ Subjects who did not report symptom in either period excluded

The significance level of the paired Wilcoxon signed rank test

Table 3: Adverse Events

Category	Mexiletine	Placebo
Cardiac	1	1
Constitutional	3	0
Dermatology/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

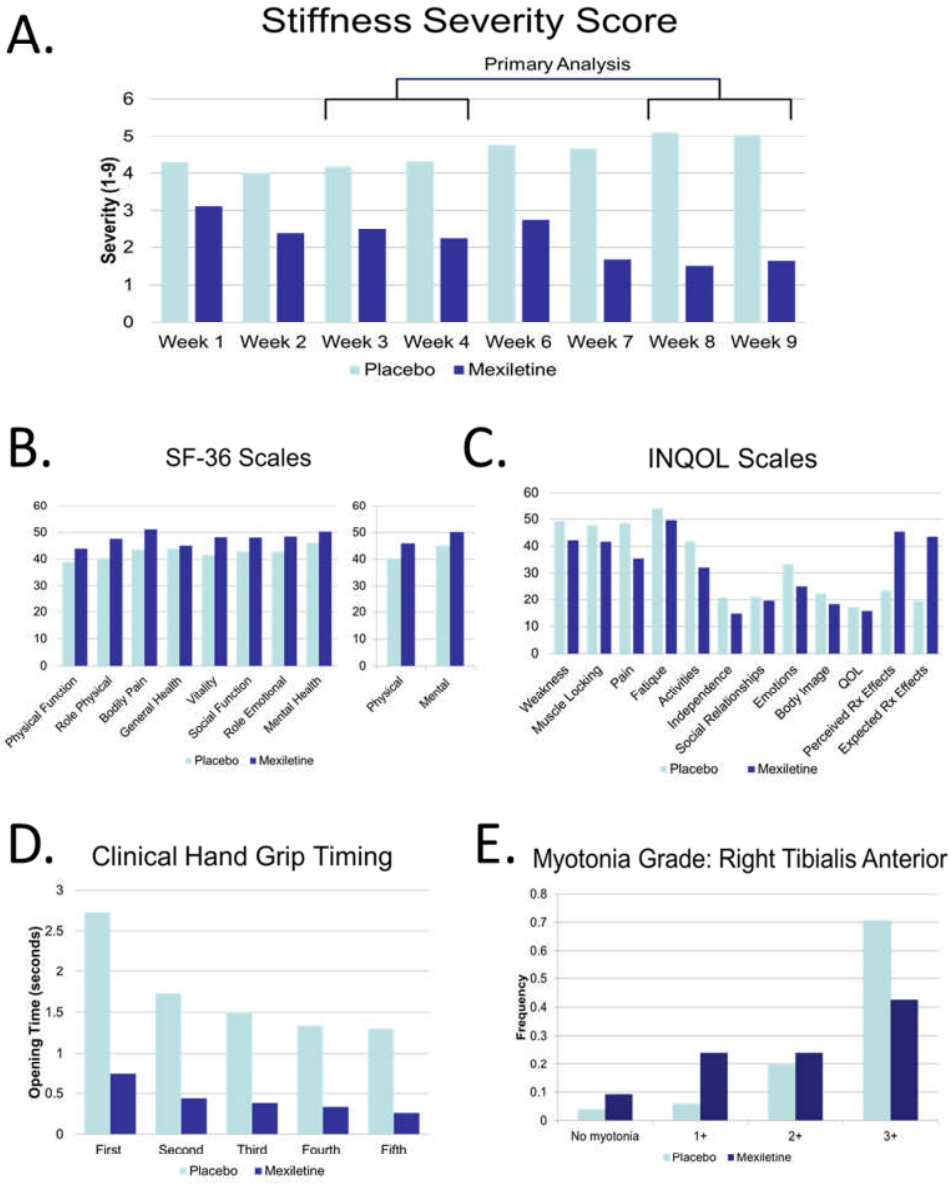


Figure 2. A. Average of IVR severity of stiffness by week (no symptom assigned zero). Significant improvements were seen in weeks 3-4 / 8-9. B. Improvement in most categories of SF-36, most notably in both physical and mental composite scores. C. Improvements in most categories of the INQoL, including the QOL score, muscle locking, and perceived treatment effects. D. Mexiletine dramatically reduces clinical handgrip relaxation times over sequential

handgrips E. Mexiletine shifts frequency of graded myotonia in right tibialis anterior to lower grades versus placebo.

Supplementary Table 1. Homogeneity testing

Endpoint	Overall Treatment Effect Estimate	Treatment Effect within Chloride*	Treatment Effect within Sodium†	Homogeneity Test
IVR—Stiffness‡	-2.69	-3.13	-2.39	0.20
IVR—Pain	-1.48	-1.48	-1.85	0.51
IVR—Weakness	-1.16	-1.14	-1.36	0.73
IVR—Tiredness	-0.900	-1.26	-0.544	0.27
SF36 – Physical Composite	5.54	6.34	5.46	0.70
SF36 – Mental Composite	4.78	6.01	3.47	0.35
INQoL - QOL	-2.69	-3.33	-2.22	0.44
Clinical assessment - eye closure (seconds)	-1.04	-0.476	-2.21	0.04
Clinical assessment – hand grip (seconds)	-1.27	-1.14	-1.77	0.58

*chloride channel mutations n=32

† sodium channel mutations n=21

‡ Primary endpoint