Guidelines on clinical presentation and management of non-dystrophic myotonias

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ABSTRACT

The non-dystrophic myotonias (NDMs) are rare muscle hyperexcitability disorders caused by gain-of-function mutations in the *SCN4A* gene or loss-of-function mutations in the *CLCN1* gene. Clinically, they are characterized by myotonia, defined as delayed muscle relaxation after voluntary contraction, which leads to symptoms of muscle stiffness, pain, fatigue, and weakness. Diagnosis is based on history and examination findings, the presence of electrical myotonia on electromyography (EMG), and genetic confirmation. In the absence of genetic confirmation, the diagnosis is supported by detailed electrophysiological testing, exclusion of other related disorders, and analysis of a variant of uncertain significance (VUS) if present. Symptomatic treatment with a sodium channel blocker, such as mexiletine, is usually the first step in management, as well as educating patients about potential anesthetic complications.

Key words: Non-dystrophic myotonias, myotonia congenita, paramyotonia congenita, skeletal muscle channelopathies, management

INTRODUCTION

The non-dystrophic myotonias (NDMs) are a group of rare monogenetic muscle disorders caused by mutations in the voltage-gated skeletal muscle sodium (*SCN4A*) or chloride ion channel (*CLCN1*) genes that lead to muscle membrane hyperexcitability.[1, 2] The clinical correlate of this muscle membrane hyperexcitability is myotonia (from the Greek words 'muscle' and 'tension'), defined as a delayed relaxation of skeletal muscles after voluntary contraction (as first described by Strümpel in 1891)[3] or after percussion (as first described by Erb).[4] Nationwide point prevalence estimates for the NDMs have been reported in the United Kingdom (0.75/100.000) and Netherlands (1.70/100.000). The prevalence is reported to be higher in some regions, probably due to founder effects and more geographically isolated populations.[5, 6] In contrast to myotonic dystrophy type 1 and 2 (DM1 and DM2), which are multi-systemic disorders with progressive muscle wasting, the NDMs are characterized by exclusive skeletal muscle dysfunction in the absence of progressive muscle wasting, and patients usually have a normal life expectancy.[7] Key patient-reported symptoms in NDMs are muscle stiffness or cramps, weakness, fatigue, and pain.[7, 8 9] Quality of life perception seems to be especially impacted by the presence of pain and fatigue.[10] Overall, quality of life measures were similar to that of patients with myotonic dystrophy (DM) and lower compared to the healthy population,[11] which justifies pharmacological treatment. Here we report guidelines created after a group of experts reviewed the literature, agreed to an outline of key concepts related to the diagnosis and management of NDM, and participated in drafting the review. We describe the pathophysiology, clinical characteristics, current approach to diagnosis, and management of these rare disorders.

TYPES OF NON-DYSTROPHIC MYOTONIAS AND RELATED DISORDERS

NDMs are first divided into two genotype groups (skeletal muscle chloride and sodium channelopathies) depending on whether the disorder is caused by a mutation in the chloride (*CLCN1*) or sodium channel gene (*SCN4A*). Historically, these disorders have then been further subdivided based on mode of inheritance, clinical or electrophysiological features (Figure 1).

Skeletal muscle chloride channelopathies, also known as myotonia congenita (MC), are subdivided based on their mode of inheritance: autosomal dominant or Thomsen myotonia congenita (TMC)[12] and autosomal recessive or Becker myotonia congenita (BMC).[13, 14] Both TMC and BMC cause muscle stiffness that can be improved with repetitive muscle activity, called the warm-up phenomenon.[15] BMC is thought to have a more severe phenotype with transient weakness that can recover after exercise.[15]

On the other hand, skeletal muscle sodium channelopathies all have autosomal dominant inheritance and can be subdivided into two major clinical phenotypes: paramyotonia congenita (PMC) and sodium channel myotonia (SCM). PMC, originally described by Eulenberg[16], is characterized by myotonia that worsens, instead of improving, with repeated muscle activity (paradoxical myotonia). In addition, the myotonia is usually cold induced and more prominent in the face compared to that seen in MC.[17] Patients with PMC can also experience episodic weakness but it is usually not the most prominent symptom. SCM is clinically characterized as a purely myotonic disorder with occasional additional features such as fluctuations in myotonia (myotonia fluctuans)[18], permanent myotonia (myotonia permanens)[19] or acetazolamide-responsiveness (acetazolamide-responsive myotonia).[20] SCM has historically been referred to as potassium-aggravated myotonia (PAM), but Rudel et al. suggested that it be referred to as SCM in the absence of a potassium loading test [21] and not all cases are potassium sensitive.

In the presence of myotonia with episodic weakness, where weakness is the most prominent symptom, the related disorder hyperkalemic periodic paralysis (HyperPP), also caused by mutations in *SCN4A*,

must be considered. HyperPP is characterized by episodes of weakness that can last hours to days, triggered by fasting, exercise, or potassium ingestion.[15] Patients with HyperPP can have myotonia, but it only occurs in about 50% of cases.[7, 8, 22] Another important disorder to recognize is severe neonatal episodic laryngospasm (SNEL) which occurs in a subset of neonatal sodium channelopathy patients. In these neonatal cases, muscle hypertonia is present along with episodic laryngospasm (especially under circumstances that initiate or aggravate myotonia such as crying or cold exposure) that can lead to life threatening periods of apnea if not diagnosed in time and treated with anti-myotonic drugs.[23]

While the focus of this review will be on the NDMs, other allelic disorders caused by mutations in *SCN4A* are reported. These diseases, caused by loss-of-function, rather than gain-of-function mutations, do not usually cause myotonia. Examples include congenital myopathy with fetal hypokinesia[24], some cases of congenital myasthenic syndrome (CMS),[25, 26] and hypokalemic periodic paralysis (HypoPP).[27]

PATHOPHYSIOLOGY

Skeletal muscle chloride channelopathies

Skeletal muscle action potentials are generated through activation of voltage-gated sodium channels that depolarize the sarcolemmal membrane. Repolarization of the sarcolemma and stability of the resting potential occur through the combined activity of potassium and chloride channels. In contrast to neurons where the resting conductance is dominated by potassium channels, chloride channels contribute the most to the resting membrane conductance in muscle.[28] The causal relationship between a reduced chloride conductance and fiber hyperexcitability with after-discharges was discovered in muscle fibers from the myotonic goat by Lipicky and Bryant in 1966. They also showed a twofold decrease in chloride permeability[29] in myotonic fibers from humans in 1971.[30 17 31] In the setting of a reduced chloride conductance, the normal activity-dependent increase of K+ concentration in the transverse tubules after muscle contraction produces an anomalously large after-depolarization of the sarcolemma.[32,33, 34] These cumulative after-depolarizations give rise to the self-sustained bursts of discharges (seen as electrical myotonia on electromyography (EMG)) that prevent the muscle from relaxing after voluntary contraction.[33, 34] However, this model does not explain why myotonia stops after a period of seconds, nor does it explain the basis of warm-up whereby with repeated activity of the same muscle the myotonia diminishes in intensity or may even cease. An additional model has been suggested where the increase in K+ causes an initial depolarization and subsequently activates a sodium persistent inward current (NaPIC) that leads to the further depolarization and generation of myotonic action potentials.[35]

Molecular genetic confirmation of the reduced chloride conductance hypothesis came in 1992 when the first mutations in the *CLCN1* gene were identified in patients with dominant and recessive MC.[1 17] Functional expression studies[36-39] and genetic cohort studies have now identified over 100 *CLCN1*-mutations.[40] The chloride channel is a dimer of ClC-1 subunits, and dominant inheritance for myotonia

congenita occurs when a mutant subunit is able to interact with a wild-type subunit to disrupt the function of the overall channel complex (dominant-negative effect). Conversely, mutations associated with recessive inheritance often result in a null allele for which the mutant subunit is not able to interact with a wild-type counterpart (e.g. non-sense mutation with a frame-shift and early termination).[41, 42] A single recessive allele is clinically asymptomatic because, as shown in pharmacologic studies with ClC-1 blockers, the chloride conductance must be reduced to less than 50% of normal to consistently produce myotonia.[31] Most of the mutations represent missense mutations (with no specific exon predominance) and around 30% represent small deletions, duplications, insertions and frameshift mutations.[5, 6] However, these mutations alone do not entirely explain each person's phenotype since family members with the same mutation can have varying disease severity.[19] Aside from the clinical variability that may occur with a loss of the chloride conductance that is at the threshold for myotonia, another source of variability may be differences in the amount of extracellular Ca^{2+} and Mg^{2+}. In rat muscle exposed to a chloride channel inhibitor, elevations in these cations have been shown to reduce myotonia through shifts in sodium channel activation.[43]

Skeletal Muscle Sodium channelopathies

All NDM sodium channelopathies are due to gain-of-function *SCN4A* mutations which either cause an increase of channel activation or a decrease of channel inactivation. These changes lead to inappropriate excitation at the end of an action potential because the availability of sodium channels is too high (impaired inactivation) or too many sodium channels are open with a mild depolarization from the resting potential (enhanced activation).[33, 34] This ability of an altered sodium current to cause myotonia was first demonstrated by application of the voltage-gated sodium channel opener veratridine (a toxin that stabilizes the open state of the channel)[44] in 1969, and, later by identifying a persistent tetrotoxin (TTX)-sensitive current that functions as a voltage-gated sodium channel blocker in muscle from patients with periodic paralysis (PP) with temperature sensitive myotonia.[45, 46] It is notable that

mutations in *SCN4A* can cause a phenotype that varies from paralysis to increased excitability (myotonia). Mutations associated with prominent defects of inactivation (larger persistent inward sodium currents and those with disrupted slow inactivation) increase the susceptibility to PP from sustained depolarization of the resting potential which inactivates the wild-type sodium channels and renders the fiber inexcitable.[47, 48] Conversely, sodium channel gain of function mutations that result in smaller persistent currents or only a transient defect (e.g. inactivation that is too slow, but eventually complete) will increase fiber excitability and lead to myotonia.

Molecular genetic confirmation of mutations in the *SCN4A* gene encoding the voltage-gated skeletal muscle sodium channel alpha subunit was first reported in HyperPP in 1991[49, 50], and in PMC[51] and SCM[52] in 1992. Functional expression studies[53] and genetic cohort studies have confirmed the pathogenicity of around 20 autosomal dominant, missense mutations in *SCN4A* causing PMC or SCM (with a hot spot in exon 22 and 24[54]) and less than ten autosomal dominant missense mutations causing HyperPP.[5, 6]

GENERAL CLINICAL PRESENTATION

Symptom onset for patients with NDM is usually in the first decade, with a slightly lower mean age of onset in patients with *SCN4A*-related myotonia.[7, 8] While NDM is sometimes thought of as a static disorder, Trip et al. found that a majority of participants reported moderate worsening of symptoms over their lifetimes.[8] The most common symptom in NDMs is muscle stiffness (myotonia), with this complaint being present in 100% of participants in one study.[7] Leg muscle stiffness is more common in chloride channelopathies and facial muscle stiffness is more common in sodium channelopathies.[7] The improvement of muscle stiffness with repeated activity, known as the warm-up phenomenon, is classically seen in MC, but is also seen in some patients with *SCN4A*-related myotonia.[7] And while cold sensitivity is generally thought of as a feature of PMC, a majority of people with chloride channelopathies report this symptom as well.[7] Other factors that have been reported to increase muscle stiffness are pregnancy or menstruation, dietary potassium (mainly in SCM), hunger, and emotional stress.[7, 54-57]

In addition to muscle stiffness, other common symptoms include weakness, pain and fatigue. Episodic muscle weakness, oftentimes triggered by cold or exercise, can occur with *SCN4A* mutations and usually lasts seconds to minutes, but can last up to 2 days.[7, 58, 59] Conversely, those with recessive chloride channel myotonia often describe weakness lasting only a few seconds, specifically when initiating movement ("transient paresis").[58] While fixed weakness and myotonia are generally considered hallmarks for DM, fixed weakness can occasionally be seen in NDM and PP.[54, 60 7] For the majority of patients the pattern of weakness or extra-muscular manifestations distinguish these disorders (see Differential Diagnosis section). That said, there are isolated families described with *SCN4A* mutations

and either distal weakness, or more profound proximal weakness.[61 62] A proportion of patients with NDM have pain as well. Although it is generally more common in sodium channelopathies, in one study pain was the most prominent symptom in about 15% of people independent of the genotype.[7] Fatigue is also common, but it is usually not the most prominent symptom.[7] The presence of pain and fatigue seem to have the greatest impact on quality of life measures.[10]

Childhood presentations of NDM are more diverse than those in adults, especially in children with *SCN4A*-related myotonia.[63] While the majority of patients presented with limb myotonia, other presenting symptoms included eyelid myotonia, double or blurred vision, strabismus and stridor or choking episodes. In addition, *SCN4A* neonates are at risk of life threatening complications due to SNEL, which usually presents with hypertonia and laryngospasm causing stridor and apnea.[23] In children with chloride channelopathies, the main symptom was leg myotonia, with 1 child having jaw myotonia causing difficulty swallowing. Leg myotonia was described by patients, parents, or clinicians as reduced running or skipping ability, frequent falls, or a "funny gait." Some patients had contractures and one of these patients developed progressive scoliosis requiring surgical intervention.[63]

Finally, anesthetic complications are well-described in both children and adults.[8, 64] These can come in the form of severe, generalized muscle spasms making intubation and mask ventilation difficult. For some people, this may even be the presenting symptom.[65] In general, multi-systemic involvement such as cardiac arrhythmias, cognitive dysfunction, respiratory muscle weakness or gastrointestinal problems are not a feature of NDM and should prompt one to consider DM as an alternative diagnosis. Some researchers have questioned whether *SCN4A* variants may sometimes be related to the development of Brugada syndrome or cardiac arrhythmogenesis, but more studies are needed.[66]

Table 1 lists important questions that should be asked as part of the patient's history.

Physical Examination

The neurological examination starts with the observation of the patient (and accompanying relatives) getting up from the chair in the waiting room, walking to the consultation room, and the strength and relaxation of the grip during a handshake. It is also necessary to note whether the patient has muscle hypertrophy, or looks like he or she exercises regularly(referred to as a Hercules-appearance in the literature). Muscle hypertrophy has been described as a typical feature of recessive MC, but can also be seen in those with a sodium channelopathy.[7]

Confirmation of clinical myotonia should be sought using myotonia bedside tests (Table 2). Action myotonia, which is commonly tested in handgrip and eyelid muscles, can be observed by watching for delayed muscle relaxation following 5-10 seconds of maximal muscle contraction.[67] Handgrip myotonia is common to both genotypes, eyelid myotonia is more common in sodium channelopathies, and leg muscle myotonia is more common in chloride channelopathies.[7] It is also valuable to evaluate for the warm-up phenomenon versus paradoxical myotonia, which may be a clue as to the type of channelopathy present. This is done by asking the patient to repeatedly tightly close and open their eyes or handgrip up to 5 times to determine whether the speed of relaxation improves (warm-up) or worsens (paramyotonia) with repetition. Delayed muscle relaxation can also be observed following mechanical stimulation of the muscle, called percussion myotonia. This is usually performed by using a reflex hammer to percuss over the thenar eminence or extensor muscles in the forearm and watching for a catch in the muscle relaxation. Other helpful signs are the presence of a transient paresis (for example of the biceps brachii muscle on bedside testing, which is unique to chloride channelopathies, and the lid-lag sign which is more typical in sodium channelopathies.[8, 68]

In general, weakness is more likely to be noted by patients than found on examination[7], possibly due to its episodic nature. One study found 17/32 PMC patients had episodic weakness but only 4/32 with fixed weakness, all at least MRC grade 4/5.[54] Trivedi et al. also found that weakness was overall mild in both genotypes and typically in a proximal distribution if present.[7] Other less common findings that may be

seen on examination, especially in children, are strabismus, scoliosis, or contractures.[15, 63, 69] While there is phenotypic overlap between the sodium and chloride channelopathies, some of the findings on history, examination, and electrophysiological testing (see *Electrophysiological Evaluation* section) are highly specific for a particular genotype. For example, the presence of paradoxical myotonia is close to 100% specific for *SCN4A*-related disorders and the presence of transient paresis was found to be 100% specific for recessive chloride channelopathies.[7, 8] While other features are not as specific, Table 3 lists potential distinguishing features between the two genotypes.

DIAGNOSIS

Diagnostic Algorithm and Criteria

Here we propose simple diagnostic criteria to help in the clinical diagnosis and to serve as a framework to support inclusion in future clinical trials (Table 4). If there is a high clinical suspicion for NDM, we recommend starting the diagnostic evaluation with an EMG to confirm the presence of electrical myotonia (especially if clinical myotonia is not obvious) followed by confirmatory genetic testing (Figure 2). In most cases, testing for both *CLCN1* and *SCN4A* mutations concurrently is suggested due to the large phenotypic overlap. If a pathogenic variant (or two pathogenic variants for BMC) is identified then there is no need for further diagnostic testing, and this would be considered a definite diagnosis of NDM. If a variant of uncertain significance (VUS) is found, then this would be considered probable NDM, and if no variant is found, it would be considered possible NDM (Table 4). If genetic testing does not identify a known pathogenic mutation, or if genetic testing is unavailable, then further diagnostic work-up is recommended and is supportive. Taken together with the history and examination, electrophysiological testing can help support the diagnosis of NDM, and even give clues as to the type of channelopathy. It is also important in this situation to exclude other disorders, especially DM (see more discussion in the *Differential Diagnosis* section). If a VUS is present, its pathogenicity can also be supported by the type of mutation and predicted effect on the channel, conservation within the genome and segregation-analysis. If available, *In vitro* analysis of the mutation can be completed as well.[70]

Genetic Testing

There is limited data on detection rates of *CLCN1* and *SCN4A* variants in patients for whom there is a high clinical suspicion of NDM. One group reported the false-negative rate to be as high as 20% in 2007.[71] However, in a large cohort of Dutch families with suspected NDMs (54 families),[70] in-tandem

single gene sequencing analysis identified at least one variant in 100% of cases. The actual mutation detection yield was thought to be, at worst, 93% due to three recessive and three sporadic cases not yielding a second *CLCN1* mutation.[70] An overview of all reported mutations of *SCN4A* and *CLCN1* is beyond the scope of this report but can be found at the LOVD (Leiden Open Variant Database).[72, 73]

Electrophysiological Evaluation

Needle EMG can be used to test for the presence of myotonic discharges (e.g. electrical myotonia). Myotonic potentials are defined as repetitive discharges, firing at a rate of 20-80 Hz, in which the amplitude and frequency of the potentials wax and wane, creating a characteristic 'dive bomber' sound.[74] The individual potentials may resemble fibrillation potentials or positive sharp waves, but it is the repetitive firing and unique sound that distinguishes it as a myotonic potential.[74] The sensitivity of myotonic discharges in NDMs and DM1 was found to be 100% if enough muscles were examined bilaterally (tibialis anterior, quadriceps, first dorsal interosseous and biceps brachii, 10 insertions per muscle).[75-77] In DM2, sensitivity of myotonic discharges using this protocol has been reported to be 100% in the largest cohort study[76], but reduced sensitivity is reported in case reports and a small cohort study.[78, 79] For these reasons, the negative predictive value of EMG in excluding a myotonic syndrome approaches 100%, but myotonia may be harder to find in DM2. However, the finding of myotonic discharges on needle EMG is not specific for a myotonic syndrome. Myotonic discharges can also be found in other neuromuscular disorders such as Pompe disease (often isolated discharges in paraspinal muscles[80]), inflammatory myopathy, congenital myopathy (especially myofibrillar myopathy[81]), rippling muscle disease[82] and anti-MuSK myasthenia gravis(for complete overview see [83]).[84] Myotonia has also been found in severe hypothyroidism (although these pre-genetic era patients might have had unrecognized DM2 in which hypothyroidism can elicit symptoms of myotonia)[85] and after the use of certain drugs: 20,25-diazacholesterol, clofibrate, 2,4-dichlorophenoxyacetate, chloroquine, colchicine and hydroxymethylgutaryl coenzyme A reductase inhibitors.[86-93] However, many of these cases may

actually be examples of "pseudomyotonia," in which complex repetitive discharges may have been confused for myotonia, and clinically symptomatic myotonia is not usually present.[74] The quantitative and qualitative differences in myotonic discharges may also be used to help discriminate between different disorders (see Table 3). For example, the duration of the first interdischarge interval of a myotonic discharge upon needle examination of the rectus femoris muscle can discriminate between sodium and chloride channelopathies with a discriminative power of >95% (where the interdischarge interval is less than 30 ms for sodium channelopathies and greater than 30 ms for chloride channelopathies).[75] In addition, electrical myotonia differs between DM1 and DM2. With the exception of proximal leg muscles, electrical myotonia is more evocable in DM1 than DM2 and tends to be waxing and waning in DM1 but only waning in DM2.[76] Finally, needle EMG can be used to identify patterns that rule out NDMs and may point towards another neuromuscular disorder. For example, myopathic changes make DM more likely, electrically silent cramps may point toward Brody disease, or a combination of myokymic and neuromyotonic discharges may indicate Isaacs' syndrome[94].

Exercise in combination with determination of compound muscle action potential amplitude or area can be helpful in situations where genetic testing is negative or indeterminate. The short exercise test (SET), first reported by Streib[95] is useful for differentiating types of NDMs from one another. It is performed by having the patient maximally contract a muscle (typically the abductor digiti minimi (ADM)) for 10-12 seconds followed by supramaximal (ulnar) nerve stimulation immediately after exercise and then every 10 seconds for 50 seconds.[96] This is repeated 3 times in succession, and after cooling and rewarming which can increase the sensitivity.[97] An abnormal decrement is defined as a concordant reduction in amplitude and area of greater than 20%.[98] Different patterns, called Fournier patterns, (see Table 5) can be distinguished from a combination of needle-EMG and SET results. Pattern I is typical in PMC patients, in whom decrements are maximal after the third trial and pattern II is common in MC patients, particularly BMC patients, in whom the maximal decrement occurs after the first trial. Pattern III, which

does not show any abnormal decrement, is typical for SCM patients.

The SET is more useful in differentiating NDMs, but positive long exercise tests (LETs) have been reported in both MC and PMC.[98, 99] The LET, first reported by McManis[100], is performed by having the patient maximally contract the ADM for 5 minutes followed by supramaximal stimulation of the ulnar nerve every minute for 40 to 60 minutes. A positive test is defined by a reduction in the compound muscle action potential (CMAP) amplitude, typically during the post-exercise period, by more than 40%. In MC and PMC patients, decrements of greater than 40% on this test have been seen, but the decrement occurred during the 5 minute exercise instead of during the period of rest.[98]

Differential Diagnosis

An alternative diagnosis should be considered if the signs or symptoms are not typical of NDM or if the diagnosis is not confirmed by genetic testing. In a patient with clinical and/or electrical myotonia, it is important to consider DM. DM1 is much more common than NDM, and in some patients the muscle weakness and systemic signs may be subtle. Clues that suggest a diagnosis of DM include frontal balding, ptosis, temporal atrophy, cardiac arrhythmias, respiratory weakness, early cataracts, gastrointestinal or cognitive dysfunction, and progressive muscle weakness.[101] In DM1, the muscle weakness usually occurs first in the neck flexors, finger flexors, and foot dorsiflexors whereas in DM2 the muscle weakness is in proximal limbs. As noted above, proximal limb weakness can be seen in NDM, but it is uncommon and rarely worse than Medical Research Council (MRC) grade 4. DM2 may be harder to distinguish from NDM, but, DM2 usually presents in adulthood, and episodic weakness is not a feature of DM2. Furthermore, pain was found to be the most prominent disease symptom in DM2, whereas complaints of muscle stiffness were less common.[7] In a subset of DM2 patients, a *CLCN1* or *SCN4A* mutation is found as a disease modifier making diagnosis more challenging.[102-104]

There are also other related disorders that need to be considered. If PP is the main symptom within the phenotype then a primary PP may be the correct alternative diagnosis. On the other hand, if certain

features are seen in addition to myotonia (or pseudomyotonia), such as mask-like facies, blepharospasm, and skeletal deformities then Schwartz-Jampel syndrome should be considered.[105, 106] Laboratory analysis can also be helpful when the diagnosis is uncertain. Creatine kinase (CK) and thyroid function tests are not discriminatory but may help to suggest an alternative diagnosis. For example, CK in NDM can typically range from normal to moderately increased (1-3 X normal), but a very high CK should lead one to investigate other causes of muscle disease.[7] In addition other muscle disorders should be considered if electrical myotonia is present without clinical myotonia. Inflammatory myopathies have been reported to have electrical myotonia or pseudomyotonia[107] but these disorders are usually easily distinguished by the clinical history. Hereditary muscle disorders such as Pompe disease, centronuclear and myofibrillar myopathies have also been reported to sometimes have electrical myotonia (see *Electrophysiological Evaluation* section for a more complete list).[107] Other hereditary muscle disorders such as Brody myopathy (caused by mutations in *ATP2A1*)[108] and rippling muscle disease (caveolinopathy caused by *CAV3* mutations)[109] may be difficult to distinguish clinically due to the similar symptoms of muscle stiffness, myalgia, cramps, and fatigue. If a hereditary myopathy is considered in the differential diagnosis, we recommend gene panel testing that includes these disorders.

Other non-muscular etiologies should also be considered. As previously mentioned, severe hypothyroidism has been associated with electrical myotonia so testing thyroid function is important.[85] Electrical myotonia has also been reported secondary to some medications (see *Electrophysiological Evaluation* section).[86-93] Another neurologic disorder to consider is Isaacs' syndrome, which is a peripheral nerve hyperexcitability disorder characterized by neuromyotonia and myokymia with symptoms of muscle stiffness, cramps, and fatigue. Neuromyotonic, rather than myotonic, potentials are seen on EMG, characterized by irregularly firing motor unit action potentials at a rate of 150-300 Hz. It is most commonly an autoimmune disorder caused by the presence of voltage-gated potassium

channel antibodies, although mutations in *KCNA1* can be responsible for the inherited form.[110, 111] Dystonia may also be considered as some of the symptoms may be similar, but the EMG should be normal.[112]

Muscle ultrasound and muscle MRI

Muscle ultrasound and muscle MRI are not currently part of the diagnostic algorithm, but may become so in the future, or may become an important part of future clinical trials. One study that evaluated muscle ultrasound in a NDM cohort found elevated echo intensities in all muscles except the rectus femoris as well as muscle hypertrophy in the arms.[113] Muscle MRI evaluation in a NDM cohort showed hyperintensity within muscles on either T1-weighted or short-T1 inversion recovery (STIR) images in all patients. Edema was common in calf musculature especially in the medial gastrocnemius muscle (18/21 patients), where a fairly specific finding of a 'central stripe' of STIR hyperintensity was observed in 10/11 *CLCN1* patients and 3/10 *SCN4A* patients but no healthy volunteers.[114]

TREATMENT AND MANAGEMENT

See Table 6 for an overview of common medications used for the treatment of NDMs.

Sodium channel blockers

Mexiletine, a class IB antiarrhythmic that works by enhancing fast inactivation of sodium channels, currently has the most evidence of effectiveness in the treatment of NDMs and received European marketing authorization through an orphan drug designation in 2018. Two independent, randomized, placebo-controlled trials have shown that mexiletine is effective in reducing patient reported muscle stiffness, weakness, tiredness, and pain.[115, 116] Mexiletine also improved quality of life scores and reduced clinical myotonia on examination. In addition to mexiletine, lamotrigine was also effective in reducing patient-reported measures of myotonia and improving quality of life scores in a single randomized, placebo-controlled trial.[117] Similar to what has been recorded in the epilepsy literature, lamotrigine was well-tolerated. In the mexiletine trials[115, 116], there was a significant difference in effectiveness in favor of the chloride channelopathy patients in comparison to the patients with a sodium channelopathy. However, the opposite was found in a long-term, retrospective clinical cohort.[118] Ranolazine, a medication FDA approved for chronic angina (European Medicines Approval (EMA) approval for add-on chronic angina treatment), is another sodium channel blocker that has recently shown effectiveness in small open-label trials. [119, 120] Instead of increasing fast-inactivation of sodium channels like mexiletine and lamotrigine, ranolazine enhances slow inactivation of sodium channels.[121] There is also level 3 evidence for the use of other sodium channel blockers such as procainamide (the oral form is not available in the United States), flecainide, phenytoin, carbamazepine, and tocainide (withdrawn from the market).[101, 122] Lacosamide and rufinamide are sodium channel blockers with reported anti-myotonic efficacy in vitro, but have not been formally studied in patients.[123]

Other pharmacological treatment

Other types of medications such as carbonic anhydrase inhibitors, antidepressants, and calcium channel blockers have been tried in the treatment of myotonia. In a small open-label study of acetazolamide (a

carbonic anhydrase inhibitor) performed prior to the availability of genetic testing, patients with MC had improvement in myotonia, but 1 out of 2 PMC patients experienced severe weakness related to the treatment.[124] And, as mentioned, one SCM phenotype is named for its responsiveness to acetazolamide.[20] It remains unclear how acetazolamide reduces symptoms of myotonia. One study suggested that acetazolamide may increase the open probability of chloride channels at the resting potential, but this has not been confirmed with further studies.[125] Also, in those with a *SCN4A* mutation and a HyperPP instead of PMC phenotype, acetazolamide or dichlorphenamide, a more potent carbonic anhydrase inhibitor, is often the treatment of choice to reduce paralytic attacks.[27, 126]

Tricyclic antidepressants have also been tried for the treatment of myotonia with some success in DM1 patients[127, 128], and may have had benefit in *SCN4A* patients as reported in a case series.[129] Other medications like nifedipine, a calcium channel blocker, and taurine, an amino acid that that stabilizes muscle membranes, have also mainly been evaluated in small trials with DM1 patients with some improvement in myotonia.[130, 131] Botulinum toxin A has been tried in one case of MC but was not effective.[132] Quinine has historically been used for the treatment of myotonia, but is no longer used due to concern for rare but severe hematological side effects.[133]

Treatment in children

No trials have been completed in children with NDM, but there are many case reports and case series using medications similar to those used in adults, [134] including mexiletine, acetazolamide, carbamazepine, and dantrolene.[135-137] One case series suggests acetazolamide as a possible first choice in children with both chloride and sodium channelopathies based on its safety and experience with the drug amongst neurologists, although with the available trial evidence in adults, mexiletine should probably be considered to be the first drug of choice for children with NDM too (expert opinion).[134] Treatment of SNEL may require special consideration, such as the monitoring of serum drug levels.

While mexiletine and carbamazepine have been used with some success[138] there is some clinical and in vitro evidence that flecainide may be most effective in this phenotype.[139] A single case described flecainide-induced Brugada Syndrome in an adult patient with *SCN4A*-related myotonia suggesting some caution, although this might have been an unrelated co-morbidity.[140]

Future Directions in Treatment

More treatment options are needed as some patients are "non-responders" to certain medications and some patients continue to have disabling symptoms despite treatment.[116] Furthermore, Trivedi et al. found that 39% of patients are not on anti-myotonic treatment[7] despite all patients reporting symptoms. It is not clear if this is because the symptoms were too mild for treatment, physicians were unaware of the possible treatment options, there was reluctance of some physicians as well as patients to start a "cardiac drug" such as mexiletine, or because of medication-related problems such as lack of efficacy, side effects, or insurance coverage issues. Future trials should help determine whether a combination of treatments can be more helpful than one medication alone as well as exploring new mechanisms for potential therapy. For example, further exploration of myotonia modifiers such as calcium and magnesium is one potential avenue[43] as is further examination of ways to increase chloride conductance, which has proven to be a challenge thus far.[141] One group is currently studying beta adrenergic drugs, which have been found to have an effect similar to mexiletine in a myotonic rat.[142] This same group is also exploring a pharmacogenetics approach to find the best medication option for a particular mutation.[143, 144] From a methodological perspective, aggregated N-of-1 trials (i.e. single patient multiple cross-over trials) can help to create the desired personalized treatment outcome estimates, with increased power due to the multiple cross-over design and use of a Bayesian hierarchical model, while also providing results on the (sub)group level(s).[116]

Behavioral modification and physical exercise

Behavioral modification is discussed with patients if specific triggers, such as cold or potassium ingestion, can be identified. Behavioral modification, in the form of diet or exercise changes, is especially important in those with a PP phenotype as detailed in a recent review.[27] The effect of physical exercise on NDM has not been studied extensively. One study of 6 people with MC found that aerobic training was not an effective anti-myotonia treatment, but it did improve fitness and CK levels remained stable.[145] In general, we tell our patients that physical exercise, especially aerobic exercise such as swimming, bicycling or walking is encouraged. If the patient is not weak, we tell people that resistance exercise is also not likely to be harmful.

Anesthetic considerations

All patients with NDM should be made aware of the potential anesthetic complications. The use of the depolarizing muscle relaxant succinylcholine should be avoided as there are many case reports of this inducing a myotonic crisis with severe generalized muscle stiffness.[64, 65] While there have been a few cases reports of malignant hyperthermia in patients with myotonia, it is not thought to be a considerable risk.[146] We advise patients with NDM to carry a medical warning card or wrist band with information of the disease and drug contraindications.

Pregnancy

A majority of patients report worsening of symptoms during pregnancy,[147] and this is likely exacerbated by having to stop medications. It may take some women months after the pregnancy to return to their baseline level of symptoms.[147] Treatment of myotonia during pregnancy should only be considered if the patient's symptoms are very severe due to the lack of safety data (i.e. category C) on the risk of teratogenicity. However, there are case reports of mexiletine and acetazolamide being used safely in pregnancy (although not specifically for NDM).[148, 149] With regards to effects on the pregnancy itself, one

study of 25 women with a total of 63 pregnancies found an increased rate of infertility and fetal distress, but overall pregnancy outcomes were benign.[147] Still, due to the possibility of life threatening complications like SNEL in *SCN4A* newborns, it is recommended that mothers discuss this risk with their obstetrician when planning a pregnancy.

CONCLUSION

Due to its rarity, there have been relatively few clinical trials and natural history studies in patients with NDM. The trials that have been completed have been helpful in creating a better understanding of the disease spectrum and the impact it has on quality of life. Due to these studies, the large phenotypic overlap has been increasingly recognized, and now there is level I evidence for the use of two medications in NDM. Still, a treatment gap exists in this population, and many patients are left with disabling symptoms even on treatment. Future studies should help to address these gaps and lead to improved patient-specific treatment. Ultimately, disease modifying treatments in the form of gene therapy are likely to be investigated for NDM, and will hopefully lead to better patient outcomes as well.

Abbreviations

ADM: abductor digiti minimi

BMC: Becker myotonia congenita

CMAP: compound muscle action potential

CMS: congenital myasthenic syndrome

DM: myotonic dystrophy

DM1: myotonic dystrophy type 1

DM2: myotonic dystrophy type 2

EMA: European Medicines Approval

EMG: electromyography

FDA: Food and Drug Adminstration

HyperPP: hyperkalemic periodic paralysis

HypoPP: hypokalemic periodic paralysis

LET: long exercise test

MC: myotonia congenita

MRC: Medical Research Council

NaPIC: sodium persistent inward current

NDM: Non-dystrophic myotonia

PAM: potassium-aggravated myotonia

PMC: paramyotonia congenita

PP: periodic paralysis

SCM: sodium channel myotonia

SET: short exercise test

SNEL: severe neonatal episodic laryngospasm

STIR: short-T1 inversion recovery

TMC: Thomsen myotonia congenita

TTX: tetrodotoxin a voltage-gated sodium channel blocker

VUS: variant of uncertain significance

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FIGURE LEGENDS

Figure 1. Classification scheme of non-dystrophic myotonias and closely related disorders

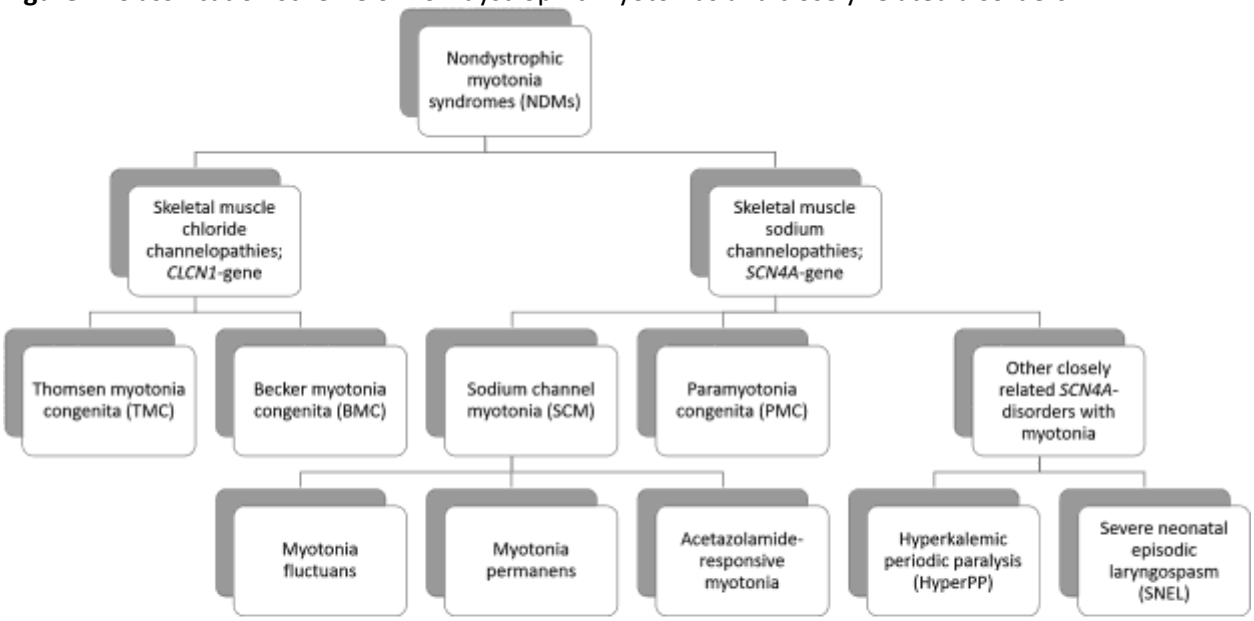
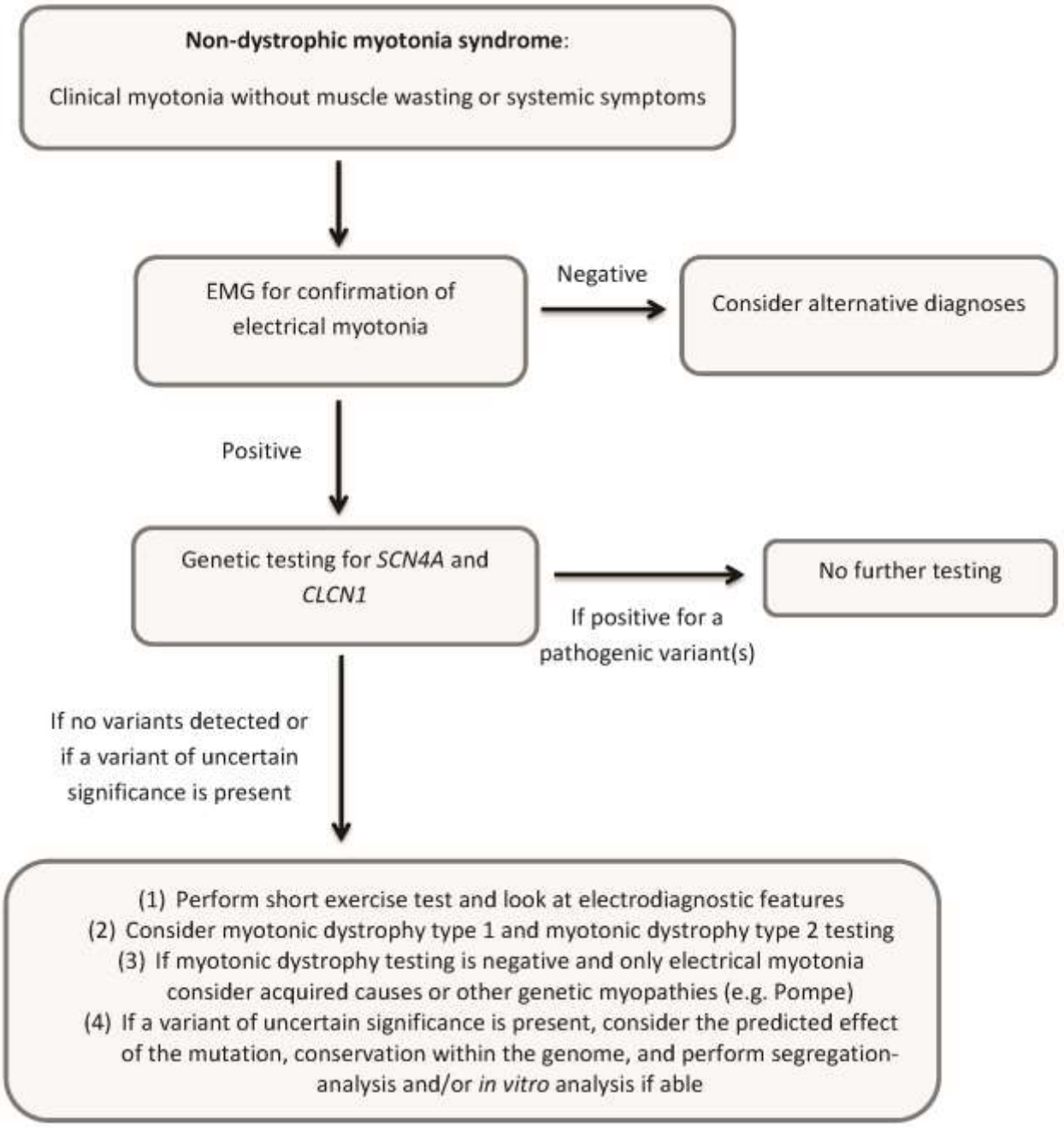


Figure 2. Diagnostic Algorithm



TABLES

Table 1. Summary of general medical history questions

What are your primary symptoms: stiffness, cramps, muscle weakness and/or pain?

- In which muscles do you experience the most stiffness? (e.g. *Eyelids, face, handgrip, legs)*
- Do you experience persistent and/or episodic muscle weakness?
- Do you notice the presence of specific triggers? *(e.g. cold environment, stress, potassium-rich foods, physical activity)*
- Did your symptoms change in intensity during pregnancy?

When did your symptoms start?

- Were there any problems at birth or during childhood (*problems breathing or feeding, episodic stridor during early childhood, whether motor milestones were met on time, ability to perform sports during childhood)*?

Have you experienced complications of general anesthesia?

Family history:

- Do you have relatives with similar complaints?
- Are your parents related?

Are there any signs of multi-systemic complaints as seen in myotonic dystrophy in the patient or relatives? *(e.g. cardiac arrhythmia, sudden cardiac death, respiratory problems, gastrointestinal problems, ptosis, cataracts, cognitive problems etc.)*

Table 2. Myotonia bedside tests

Percussion myotonia in thenar, forearm extensor, trapezius, quadriceps and tongue muscles
Action myotonia of handgrip, eyelid closure, quadriceps muscles *(5-10 sec maximal voluntary contraction - repeated 5 times to check for warm-up phenomenon or paradoxical myotonia)*
Transient paresis test in biceps[8]
Lid-lag sign and extra-ocular muscle myotonia causing short-term diplopia[68]

Table 3. Clinical characteristics that may help distinguish between non-dystrophic myotonia genotypes

	Sodium channelopathies	Chloride channelopathies
Clinical clues		
	Lower mean age at onset (*mean 5 years*)	Higher mean age at onset (*mean 10 years*)
	Worsening of stiffness after repetitive use/ muscle contractions (*i.e., paramyotonia*)	Decrease of myotonia after repetitive use/muscle contractions (*i.e., warm-up phenomenon*)
	Presence of pain	Lack of pain
	Presence of face stiffness	Presence of leg stiffness (*e.g., difficulty in standing up quickly, climbing stairs*)
	Episodic weakness	Transient paresis at the onset of activity (usually recessive disease)
	Worsening of symptoms in the cold	
Examination		
	Eyelid myotonia	Action/percussion myotonia in leg muscles
	Increase of myotonia after repetitive contractions (*i.e., paramyotonia*)	Decrease of myotonia after repetitive contractions (*i.e., warm-up phenomenon*)
		Transient paresis positive in biceps[8]
Electrophysiological Findings		
	Long duration (>2 s), high amplitude (>4 mV) myotonic potentials with a "slowly decelerating motorcycle" sound	Short duration (<1 s), low amplitude (<0.4 mV) myotonic potentials with a "dive bomber" sound[75]
	Interdischarge interval of myotonic potentials < 30 ms	Interdischarge Interval of myotonic potentials > 30 ms
	Fournier Pattern I or III with short-exercise testing	Fournier Pattern II with short-exercising testing

Table 4. Diagnostic Criteria for non-dystrophic myotonias

Presence of:

1. Consistent history and examination
2. EMG with myotonia
3. Genetic confirmation of a known pathogenic variant(s) in *SCN4A* or *CLCN1*

Absence of: Signs and symptoms consistent with myotonic dystrophy or other potential causes of myotonia (e.g., medications).

Definite NDM**:** Must have 1 and/or 2, **and** 3

Probable NDM**:** Must have 1 and 2, **and** a VUS OR 1 or 2 are atypical **and** 3

Possible NDM: Must have 1 and 2

NDM: non-dystrophic myotonia; VUS: variant of uncertain significance

Table 5: Short exercise test - Fournier pattern description and sensitivity/specificity data

		Fournier et al.[96] * ***(healthy controls n=41, NDMs n=30, PP n=21)***	**Tan et al.[98] ** ***(healthy controls n=65, NDMs n=47, PP n=19)***
Pattern I	Electrical myotonia and post-exercise myotonic potentials (PEMPs) with significant post-exercise decrease in CMAP amplitude that worsened with repeating exercise	**PMC:** 100% sens., spec. 100%***	**PMC:** 100% sens., spec. 100%***
Pattern II	Electrical myotonia with significant transient decreased CMAP amplitude after short exercise that disappeared with repeating exercise	**MC:** 83% sens., spec. 84% (8/51)	**MC:** 72% sens. and 100% spec.
Pattern III	Electrical myotonia not associated with significant post-exercise CMAP changes	**SCM:** 50% sens., spec. 74% (12/51)	**SCM**: 100% sens., spec. (?)

NDMs: non-dystrophic myotonias; PMC: paramyotonia congenita; MC: myotonia congenita; SCM: sodium channel myotonia; CMAP: compound muscle action potential; sens: sensitivity; spec: specificity

** Significance threshold defined by a mean ± 2 SD from healthy population outcomes.*

*** Significance threshold defined by concordant amplitude and area (CAA) decrement >20%, includes refined exercise testing with pre-cooling and rewarming of the other hand.*

**** Specificity for a certain phenotype is calculated as 1 – (% of patients within the cohort of skeletal muscle channelopathies with a positive test results and a different phenotype). In comparison with the healthy controls, specificity was found to be 100% in all cases (none of the healthy volunteers exhibited an abnormal Fournier pattern).*

Table 6. Common medications used for the treatment of non-dystrophic myotonias (Adapted by permission from Springer Nature: Neurotherapeutics, Phillips and Trivedi, 2018[58])

Drug	Level of evidence	Regulatory Approval	Dosage	Side-effects	Monitoring	Other considerations
Mexiletine	Double-blind, placebo-controlled, randomized trials[115, 116]	EMA approval as orphan drug designation for NDMs	Start 150 mg BID with titration to 200 mg TID or occasionally 300 mg TID	GI discomfort, dizziness, tremor, ataxia	ECG, LFTs, consider CBC	If ECG abnormal or history of arrhythmia, consult with cardiology prior to use
Lamotrigine	Double-blind, placebo-controlled randomized trial[117]	None	Start 25 mg daily with slow titration to 300 mg daily	Skin rash, headache, fatigue, nausea	LFTs, BUN/Cr	
Acetazolamide	Non-randomized, open-label trial[58, 124]	None	125 mg BID with titration to 250 mg TID	Nephrolithiasis, paresthesias, rash, agranulocytosis, electrolyte abnormalities, GI discomfort	Basic metabolic panel (Na, K, CO_2), LFTs, CBC	Do not use if sulfa allergy. Consider renal ultrasound monitoring if high risk of nephrolithiasis.
Ranolazine	Non-randomized, open-label trials[119, 120]	None	Start 500 mg BID then titrate to 1000 mg BID	Constipation, dizziness, headache,	EKG, BUN/Cr if renal impairment.	Do not use with simvastatin > 20 mg. Limit dose to 500 mg with concurrent use of CYP3A4 inhibitors (e.g., diltiazem, verapamil)

EMA: European Medicines Agency; FDA: Food and Drug Administration; NDMs: non-dystrophic myotonias; BID: twice daily; TID: three times daily; GI: gastrointestinal; ECG: electrocardiogram; LFTs: liver function tests; CBC: complete blood count; BUN: blood urea nitrogen; Cr: creatinine; Na: sodium; K: potassium; CO_2: carbon dioxide