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Dr Johnson has served as a consultant for AMO Pharma; Asklepios BioPharmaceutical, Inc (AskBio); AveXis, Inc; Dyne Therapeutics; Fulcrum Therapeutics; ML Bio; and Vertex Pharmaceuticals Incorporated and has received personal compensation for speaking engagements from Sarepta Therapeutics and Strongbridge Biopharma plc. Dr Johnson has received research/grant support from AMO Pharma; AveXis, Inc; the Coalition to Cure Calpain 3; CSL Behring; Fulcrum Therapeutics; the Muscular Dystrophy Association; the Myotonic Dystrophy Foundation; the National Institute of Neurological Disorders and Stroke (K23NS091511-05; R01NS104010-01); Sarepta Therapeutics; and the US Food and Drug Administration (1RO1FD006071-02). Dr Johnson has received publishing royalties from the Charcot-Marie-Tooth Health Index and the Congenital and Childhood Myotonic Dystrophy Health Index.

**UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:**
Dr Johnson discusses the unlabeled/investigational use of mexiletine for the treatment of myotonia and armodafinil and modafinil for the treatment of daytime sleepiness in myotonic dystrophy.



# Myotonic Muscular Dystrophies

By Nicholas E. Johnson, MD, MSc, FAAN

## ABSTRACT

**PURPOSE OF REVIEW: This article describes the clinical features, pathogenesis, prevalence, diagnosis, and management of myotonic dystrophy type 1 and myotonic dystrophy type 2.**

**RECENT FINDINGS: The prevalence of myotonic dystrophy type 1 is better understood than the prevalence of myotonic dystrophy type 2, and new evidence indicates that the risk of cancer is increased in patients with the myotonic dystrophies. In addition, descriptions of the clinical symptoms and relative risks of comorbidities such as cardiac arrhythmias associated with myotonic dystrophy type 1 have been improved.**

**SUMMARY: Myotonic dystrophy type 1 and myotonic dystrophy type 2 are both characterized by progressive muscle weakness, early-onset cataracts, and myotonia. However, both disorders have multisystem manifestations that require a comprehensive management plan. While no disease-modifying therapies have yet been identified, advances in therapeutic development have a promising future.**

## INTRODUCTION

The myotonic muscular dystrophies are autosomal dominant disorders characterized by a clinical triad of progressive weakness, myotonia, and early-onset cataracts. The clinical features of myotonic dystrophy were originally described by Steinert in the early 1900s.[1] It was not until the late 20th century that myotonic dystrophy type 2 (DM2) was recognized as a distinct clinical entity.[2] The clinical features of myotonic dystrophy type 1 (DM1) and DM2 are summarized in TABLE 8-1. DM1 causes distal weakness in the long finger flexors, facial muscles, and ankle dorsiflexors. The myotonia (delayed muscle relaxation) is easier to evoke both clinically and electrodiagnostically in DM1 than in DM2.[3] Individuals with DM2 are more likely to have proximal weakness and prominent muscle pain. Despite these differences, both disorders can cause multisystem manifestations in the brain, heart, gastrointestinal system, skin, and endocrine and respiratory systems. These pleiotropic manifestations may present challenges to clinicians presented with these patients, as the initial symptoms may be neurologic, cardiac, or gastrointestinal, among others. Prior registry data suggest that it takes approximately 7 years for a patient with DM1 and 14 years for a patient with DM2 to receive the appropriate diagnosis.[4] Early recognition of the variety of symptoms at presentation will assist in reducing the time to diagnosis.

DM1 is the most common form of muscular dystrophy, with an estimated prevalence of 1 per 2500. This prevalence estimate is derived from individuals with a repeat expansion at birth and is higher than previous prevalence estimates (5 to 20 per 100,000), which used clinical ascertainment to guide prevalence studies.[1] The exact prevalence of DM2 is unknown, but it is likely underdiagnosed in the general population. A genetic sampling on 4532 healthy participants and 920 patients with nonmyotonic myopathies suggests the prevalence may be as high as 1 per 1830.[5]

Several studies have shown the median age of death to be in the early fifties in DM1.[6,7] The primary causes of death include cardiac arrhythmias, respiratory failure, and cancer.[6,7] Studies have not yet been conducted to determine whether patients with DM2 are at risk of a shortened life span.

## PATHOGENESIS

Both DM1 and DM2 are caused by a repeat expansion that sequesters RNA-binding proteins and results in misregulated alternate splicing. The widespread misregulation of alternate splicing is likely the cause of the diverse symptoms associated with both diseases. This RNA toxicity is an unusual pathogenic mechanism but may provide novel therapeutic strategies in drug development.

### Myotonic Dystrophy Type 1

DM1 is the result of a CTG repeat expansion in the 3′ untranslated region of the DM1 protein kinase (*DMPK*) gene on chromosome 19q13.3.[8–10] This repeat expansion is unstable both in germline and somatic cell divisions.[11]

Wide variation exists in the CTG repeat lengths that cause disease. As such, correlations between the CTG repeat length and overall disease severity are modest.[12] The CTG repeat length varies widely by organ system, which is one reason for the weak correlation.[13] The CTG repeat is more stable in leukocytes than in skeletal muscle, so the repeat length measured on a blood test is likely to underrepresent the true burden of the CTG repeat in other organ systems. Recent studies demonstrating that interruptions in the CTG repeat may modulate disease severity further hinder the ability to accurately predict the relationship between the repeat and clinical phenotype.[14] Generally, larger repeat expansions are associated with a more severe course. Individuals with repeat expansions between 50 and 150 are likely to have late onset, also known as *oligosymptomatic*

**Comparison of the Myotonic Dystrophies** TABLE 8-1

| | Myotonic Dystrophy Type 1 | Myotonic Dystrophy Type 2 |
|---|---|---|
| **Prevalence** | 1 per 2500 | Unknown |
| **Gene mutation** | CTG repeat in 3' untranslated region of the *DMPK* gene | Intronic CCTG repeat in the *CNBP* gene |
| **Age of onset** | Birth to adulthood | Early to late adulthood |
| **Pattern of weakness** | Distal muscles, face | Proximal muscles |
| **Myotonia/pain** | Prominent myotonia | Prominent pain |

*DM1*. These individuals are most likely to develop symptoms after the age of 50 and have minimal symptoms overall. Individuals with repeat lengths between 150 and 1000 are most likely to have adult-onset DM1, defined as symptom onset after age 18. Individuals with repeat lengths over 500 may have either congenital myotonic dystrophy (present at birth) or childhood-onset myotonic dystrophy (defined as having onset between 1 and 18 years of age). Overlap exists between the expected CTG repeat length and the described variants, reinforcing the absence of a strong correlation with the CTG repeat length.

The core pathogenic feature of DM1 is the intranuclear sequestration of RNA-binding proteins with the toxic RNA repeat.[15,16] When the CTG repeat in the DNA is transcribed to a CUG repeat in the RNA, the RNA repeat expansion sequesters these RNA-binding proteins and thereby disrupts the splicing mechanism, leading to a wide array of proteins that are mis-spliced and therefore nonfunctional. Several RNA-binding proteins, including muscleblind like splicing regulator 1 (MBNL1) have been shown to be co-located in foci with the CUG repeat expansion.[17,18] As a result, more than 2000 different proteins have a retained fetal pattern of RNA splicing.[19] Some of these splicing events are directly linked to the clinical manifestations. For example, loss of the chloride channel leads to myotonia (FIGURE 8-1),[20] and loss of the insulin receptor is associated with insulin resistance.[21] The direct connection between many of these RNA splicing events and the clinical manifestations is not known.

### Myotonic Dystrophy Type 2

Many similarities exist in the pathogenesis of DM2 as in DM1. DM2 is the result of an unstable tetranucleotide repeat expansion (CCTG) in the first intron of the *CNBP* gene on chromosome 3q21.[2,22,23] As with DM1, the repeat expansion has been shown to sequester RNA-binding proteins such as MBNL1, leading to massively dysregulated RNA splicing.[24] Also, the CCTG repeat expansion is somatically unstable and increases over time.[25]

However, some differences from DM1 are seen. The repeat expansion in DM2 can vary widely from 75 to well over 11,000 repeats.[26] No correlation exists between disease severity and the repeat length in DM2. Anticipation does not occur in DM2, and only a single case of congenital disease has been reported in DM2. Also, while loss of the *DMPK* gene in DM1 does not appear to cause any

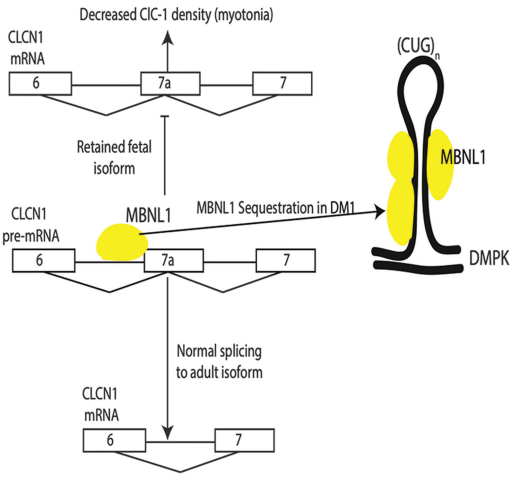


**FIGURE 8-1**

**Schematic demonstrating the pathogenesis of myotonic dystrophy type 1 (DM1). The toxic RNA repeat expansion in the *DMPK* mRNA is shown on the right side. Here, it binds to the RNA-binding protein MBNL1 (*yellow areas*). On the left side of the figure, the lower half demonstrates the appropriate splicing of the skeletal muscle chloride channel in the presence of MBNL1. The upper half shows that the loss of MBNL1 results in fetal retention of the transcript and loss of the chloride channel, which results in clinical myotonia.**

ClC-1 = chloride channel; $(CUG)_n$ = CUG repeat; mRNA = messenger RNA.

untoward effects, early evidence indicates that loss of the *CNBP* gene may have muscle toxicity as well, and therefore, loss of function of the protein may contribute to the pathogenesis.[27]

## CLINICAL FEATURES

In addition to a shared pathogenesis related to RNA toxicity, both DM1 and DM2 share several core clinical features. Both conditions lead to muscle weakness, myotonia, and early-onset cataracts. However, the pattern of weakness and other associated features are distinct between the conditions.

### Myotonic Dystrophy Type 1

The clinical triad associated with DM1 is distal muscle weakness, myotonia, and early-onset cataracts, but other features are also associated with the disease. The skeletal muscle weakness involves the distal finger flexors, ankle dorsiflexors, and facial muscles, although, over time, the weakness can progress to involve any muscle. The distal finger flexors are often affected first. Along with the progressive muscle weakness, muscle atrophy is prominent. In the facial muscles, patients will often present with bifacial weakness and mild ptosis. Myotonia can be prominent in DM1, and often involves the hands and tongue. Patients may describe myotonia as muscle stiffness or delayed muscle relaxation. The myotonia is often worse with cold or stress and may improve with use. It may be seen on physical examination by asking the patient to squeeze his or her hand tightly for 5 seconds and then open quickly, with the clinician monitoring for delayed relaxation. Percussion of the thenar eminence, forearm extensors, or tongue may also produce myotonia. Insertion of an EMG needle into the muscle may result in the characteristic "dive-bomber" sound of waxing and waning myotonia. One study demonstrated that myotonia may be seen in all muscles tested in individuals with DM1, although it is more pronounced in distal muscles.[3] Although associated with skeletal muscle manifestations, myotonia may also be associated with gastrointestinal symptoms described below.

Cardiac manifestations of DM1 include cardiac conduction abnormalities, most often progressive atrioventricular block, and are the leading cause of death in the disease.[6,28] Other cardiac arrhythmias include sinus node dysfunction, atrial or ventricular fibrillation, and atrial flutter.[28,29] Although prior studies have associated advancing age as a concomitant risk factor, new studies showing these arrhythmias in the pediatric population suggest that the conduction disorders may not be associated with advanced age.[28,30] Symptomatic heart failure is not known to be associated with DM1, although patients may have asymptomatic diastolic dysfunction.

The most impactful symptom in DM1 is fatigue, which may be driven by a combination of sleep apnea, respiratory failure, and excessive daytime sleepiness.[12] It is likely that fatigue associated with the muscle weakness contributes as well. Individuals with DM1 are at an increased risk of developing sleep apnea,[6] commonly the obstructive type, although patients with DM1 may have central sleep apnea or even narcolepsy. In addition to sleep-disordered breathing, patients with more advanced DM1 may have daytime respiratory failure (CASE 8-1).

The development of cataracts before the age of 50 is a cardinal feature of DM1. These cataracts may be either anterior or posterior subcapsular in nature and are often described as "Christmas tree" cataracts. In addition to the cataracts, corneal

**KEY POINTS**

- The myotonic muscular dystrophies are autosomal dominant disorders characterized by a clinical triad of progressive weakness, myotonia, and early-onset cataracts.
- Myotonic dystrophy type 1 is the most common form of muscular dystrophy.
- Myotonic dystrophy type 1 is caused by a CTG repeat expansion in the 3′ untranslated region of the *DMPK* gene. Myotonic dystrophy type 2 is caused by an intronic CCTG repeat expansion in the *CNBP* gene.
- The clinical triad associated with myotonic dystrophy type 1 is distal muscle weakness, myotonia, and early-onset cataracts.
- Cardiac arrhythmias, such as atrioventricular block, are the leading cause of death in myotonic dystrophy type 1.
- The most impactful symptom in myotonic dystrophy type 1 is fatigue, which may be driven by a combination of sleep apnea, respiratory failure, and excessive daytime sleepiness.

## CASE 8-1

**A 35-year-old woman presented with daytime somnolence and fatigue. She had been falling asleep at work, and her employer was concerned about her performance. Her family history was significant for a brother who had sudden cardiac death in his twenties. Her father had cataracts when he was in his forties but was otherwise healthy. On review of systems, she reported stiffness in her hands for the past 10 years and difficulty opening jars or bottles for the past 2 years.**

**Neurologic examination was significant for mild bilateral ptosis. She had 4+/5 strength in her distal finger flexors and 3 seconds of grip myotonia. The remainder of her examination was normal. Her creatine kinase level was 350 U/L. Needle EMG disclosed waxing and waning myotonia in her first dorsal interosseus. Gene testing revealed 250 CTG repeats in the *DMPK* gene.**

**COMMENT**

This is a typical presentation for adult-onset myotonic dystrophy type 1 (DM1). It is important to remember that distal muscle weakness is slowly progressive and may not be discernible for several years. Fatigue and daytime sleepiness cause significant morbidity in DM1 and may be the presenting symptoms. With smaller repeat expansions, a family history of DM1 may be difficult to discern, particularly in parents. In this case, early-onset cataracts were the only potential sign that the patient's father may be affected.

## CASE 8-2

**A pediatric neurologic consultation was requested on a 2-week-old girl with hypotonia in the neonatal intensive care unit. Her mother had a normal pregnancy and delivery, but at birth, the baby was hypoxic and was placed on a ventilator. She had continued to require a ventilator and feeding tube. On examination, she was hypotonic and hyporeflexic. She had a poor gag reflex and bilateral talipes equinovarus.**

**Despite the absence of a relevant family history, on assessment of her mother, trace grip myotonia with otherwise normal strength was noted. The baby had a normal nerve conduction study and needle EMG. Genetic testing of the baby disclosed 1000 CTG repeats on the *DMPK* gene.**

**COMMENT**

This baby has congenital myotonic dystrophy. Rapid and significant expansion of the CTG repeat can result in large intergenerational expansions, known as anticipation. It is important to note that mothers may be asymptomatic or nearly asymptomatic, limiting opportunities for prenatal counseling. The available data suggest that most infants with congenital myotonic dystrophy are able to wean from the ventilator, feed orally, and achieve developmental milestones. Parents should be counseled about this gradual improvement, with the appropriate context regarding the significant morbidity associated with the disease.

abrasions may occur because of an inability to close the eyes at night due to the bifacial weakness. Sensorineural hearing loss has been reported in DM1, although it is uncommon for patients to require hearing aids.

The cognitive impairment in DM1 can vary widely. Patients may range from having no cognitive impairment to global intellectual impairment.[31] Most commonly, executive function and visuospatial processing are impacted.[32] In addition to the cognitive symptoms, patients may have an avoidant personality disorder and apathy, as well as a higher risk of depression.[33] Brain MRI may reveal atrophy, particularly of the frontal and parietal regions.[34] White matter lesions are also commonly seen.

Patients with DM1 may have dysphagia, dysarthria, and gastroesophageal reflux. The dysarthria and dysphagia are related to a combination of muscle weakness and myotonia. They may also have constipation, diarrhea, abdominal pain, or bloating. This symptom constellation is similar to irritable bowel syndrome, although it is more likely related to smooth muscle myotonia of the gastrointestinal system.

A number of endocrine disturbances are seen in DM1. These include insulin resistance, hypogonadism, and thyroid disturbance. Patients with DM1 commonly have modestly elevated creatine kinase (less than 500 U/L), liver enzymes, and cholesterol levels.[35]

Recent evidence suggests that patients with myotonic dystrophy are at an increased risk of cancer. This is based on five different epidemiologic studies.[36] Since these data come from registry data sets without significant identifying information, it is currently unclear as to which patient characteristics contribute to this increased risk. While the exact types of cancer that have been demonstrated to have an increased risk vary by study, many studies have noted cancer of the reproductive tract (endometrial, ovarian, and testicular), as well as melanoma and thyroid and colorectal cancers.[6,37,38]

**CONGENITAL AND CHILDHOOD-ONSET MYOTONIC DYSTROPHY TYPE 1.** Rapid expansion of the CTG repeat between generations can result in the development of symptoms early in life. Although the exact reason is unknown, this repeat expansion tends to be most significant when it is passed from mother to child rather than from father to child.[1] If the symptoms begin at birth, it is called *congenital myotonic dystrophy*. Neonatal manifestations often include hypotonia, respiratory failure, feeding problems, and talipes equinovarus (clubfoot), although it is uncommon for all symptoms to be present. The respiratory failure may require mechanical ventilation, and children ventilated for longer than 3 months have a 30% mortality in the first year of life.[39] Interestingly, all these neonatal symptoms resolve over a period of several years, and the majority of these children (although not all) are eventually able to ambulate, breathe without support, and eat orally (CASE 8-2).[30,40,41]

Common manifestations of congenital myotonic dystrophy through childhood include intellectual impairment, attention deficit hyperactivity disorder, and autism spectrum disorders.[30,40,42–44] Children may have profound gastrointestinal symptoms, including diarrhea, constipation, and fecal incontinence. The typical adult symptoms described above often do not manifest until adolescence.

Childhood-onset myotonic dystrophy is defined as symptom onset after the age of 1 and before the age of 10. These early childhood symptoms often include

**KEY POINTS**

- **Patients with myotonic dystrophy type 1 may have a symptom complex similar to irritable bowel syndrome.**
- **If the symptoms of myotonic dystrophy type 1 begin at birth, it is called *congenital myotonic dystrophy*. The neonatal manifestations often include hypotonia, respiratory failure, feeding problems, and talipes equinovarus (clubfoot).**

## CASE 8-3

**A 45-year-old man presented with proximal muscle pain and arm weakness. He reported that he had been diagnosed with fibromyalgia because of significant proximal muscle pain and tenderness for the past 15 years. Recently, he had experienced difficulty putting dishes away on high shelves. He denied difficulty getting up from a chair or walking. His family history was significant for a father who had "some form of muscular dystrophy" and was in a wheelchair at the end of his life. He had two sisters who also were diagnosed with fibromyalgia.**

**His neurologic examination was significant for 4+/5 neck flexion strength and 4/5 shoulder abduction strength bilaterally. He had no percussion or grip myotonia. The remainder of his examination was normal. Needle EMG disclosed occasional waning myotonia in the shoulder abductors but was otherwise normal. Gene testing disclosed 11,000 repeats in the *CNBP* gene.**

**COMMENT**

This patient has myotonic dystrophy type 2 (DM2). Patients with DM2 may have proximal pain long before muscle weakness develops, leading to an early diagnosis of fibromyalgia or other chronic pain syndrome. The myotonia in DM2 may be indiscernible on examination and difficult to detect on needle EMG. The case illustrates the need to continue to investigate DM2 in patients with proximal weakness and muscle pain.

**TABLE 8-2** Screening Tests and Their Frequencies for the Myotonic Dystrophies

| Symptom Domain | Screening Test | Frequency | Myotonic Dystrophy Type |
|---|---|---|---|
| **Heart** | ECG[a] | At diagnosis and annually | Both type 1 and type 2 |
| **Eyes** | Slit-lamp examination | At diagnosis and annually | Both type 1 and type 2 |
| **Lungs** | Clinical examination and supine forced vital capacity | At diagnosis and annually | Type 1 more common than type 2 |
| **Sleep** | Polysomnogram | At diagnosis and with symptoms | Type 1 more common than type 2 |
| **Endocrine** | Screening thyroid-stimulating hormone (TSH), lipid panel, hemoglobin $A_{1c}$ | At diagnosis and either annually (TSH and hemoglobin $A_{1c}$) or every 3 years (lipid panel) | Type 1 more common than type 2 |
| **Brain** | Clinical history and examination to screen for memory and psychological concerns | At diagnosis and annually | Type 1 more common than type 2 |
| **Cancer** | Appropriate age- and gender-based screening tests | As recommended for age and sex | Both type 1 and type 2 |

ECG = electrocardiogram.
[a] The ECG is the minimum screening test. Practice may vary and care guidelines may recommend Holter or loop recorders depending on the patient.

the intellectual impairment and gastrointestinal symptoms described earlier. Patients with either congenital or childhood-onset myotonic dystrophy are expected to have a more severe course than those with adult onset. Recent research indicates that the same RNA splicing dysregulation is the cause, so these classifications are best thought of as a continuum of disease severity from congenital to childhood, adult, and late onset.[45]

### Myotonic Dystrophy Type 2

Muscle weakness in DM2 is predominantly proximal rather than distal and includes the neck flexors, hip flexors, and hip extensors. Myotonia, as seen in DM1, is less common in DM2. It can be more difficult to detect on physical examination but can be seen proximally.[40] Similarly, waning myotonia may be seen on electrodiagnostic testing but is less frequently found.[3]

However, pain is prominent and severe in DM2 (CASE 8-3). The pain is also proximal and often described as aching or stiff. Indeed, 79% of survey respondents reported significant pain.[46] It is possible that this pain may be diagnosed as fibromyalgia in the absence of other DM2-associated features. The pain fluctuates in intensity and can be provoked by exercise, palpation, or cold temperature.[47]

Cardiac conduction disturbances are less frequent in DM2 than in DM1 but may occur, and cases of sudden cardiac death have been reported.[48,49] Patients with DM2 may also have impaired sleep. This is more likely due to poor sleep quality than to sleep apnea.[50] Impaired sleep quality is thought to be associated with chronic pain in DM2. A dysexecutive syndrome has been reported in DM2 as well as an avoidant personality.[51] Global intellectual impairment is uncommon. Patients with DM2 have modestly elevated creatine kinase levels similar to DM1 as well as elevations of liver enzymes.[52] They are at risk for the development of diabetes mellitus, similar to patients with DM1.

KEY POINTS

- Childhood-onset myotonic dystrophy is defined as symptoms after the age of 1 and before the age of 10. These early childhood symptoms often include intellectual impairment and gastrointestinal symptoms.
- Muscle weakness in myotonic dystrophy type 2 is predominantly proximal rather than distal and includes the neck flexors, hip flexors, and hip extensors.
- It is possible that pain may be diagnosed as fibromyalgia in the absence of other myotonic dystrophy type 2–associated features.

## MANAGEMENT AND TREATMENT

The management of DM1 and DM2 requires a multidisciplinary plan with a number of routine screening tests to prevent the array of complications that may arise in these conditions (TABLE 8-2).

### Diagnosis and Genetic Counseling

The gold standard test for both DM1 and DM2 is DNA testing to identify the CTG or CCTG repeat expansions in the blood.[53] This is required to confirm the diagnosis in the proband. However, as this is an autosomal dominant disorder, many clinicians will defer genetic testing in first-degree family members with associated symptoms and signs. Electrodiagnostic testing can be useful in these situations, as electrical myotonia may be present even without clinical myotonia.[3] Muscle biopsies, however, are generally nonspecific. In patients with DM1, muscle biopsy may demonstrate increased central nuclei, angular fibers, atrophy, and pyknotic clumps, while in DM2, the muscle biopsy is often normal or may demonstrate fiber size variation.

Patients often benefit from genetic counseling on the inheritance pattern, including that subsequent generations may be at risk of a repeat expansion that will result in more severe symptoms in the offspring. In DM1, this risk is most significant when the mother passes the repeat expansion, although anticipation also occurs, to a lesser degree, with paternal transmission. In contrast, anticipation is not significant in DM2. Patients considering having children

should be aware that in vitro fertilization with preimplantation diagnosis is an option to ensure that offspring will not carry the repeat expansion.

### Skeletal Muscle and Myotonia Management

Patients with DM1 or DM2 should be evaluated on an annual basis for difficulty with mobility and screened for falls. Both patients with DM1 and patients with DM2 benefit from moderate-intensity aerobic exercise.[53,54] Patients may also require home or environmental modifications over time. In addition, patients may require intermittent evaluations by physical therapists or occupational therapists for assistance with orthotics, assistive devices, or modification in activities of daily living.

In particular, patients with DM1 often require ankle-foot orthoses relatively early in the disease course given the prominent dorsiflexion weakness. Patients with either DM1 or DM2 may require canes, walkers, wheelchairs, or other assistive devices.

Skeletal muscle myotonia may be treated with several different agents that target skeletal muscle sodium channels. The best studied is mexiletine, which has been shown to reduce the myotonia in patients with DM1.[55] Ongoing studies are assessing the potential cardiac side effects of mexiletine. While other agents have been less studied, anecdotal evidence exists for the use of medications such as phenytoin, carbamazepine, amitriptyline, and acetazolamide. While the myotonia in DM2 is often less prominent, it can be treated with the same approach. The proximal pain symptoms seen in DM2 may have a component of myotonia; therefore, antimyotonia agents may be helpful. However, they are typically insufficient to treat the pain. Given the potential respiratory concerns, opioid class medications are not recommended. In addition to medications targeting the myotonia, medications that have been shown to effectively treat the pain associated with fibromyalgia may be helpful.

### Cardiac Management

Patients with DM1 or DM2 are at an increased risk of developing life-threatening cardiac arrhythmias. It is recommended that patients have an ECG at diagnosis and annually thereafter.[53] Patients should be screened for the presence of palpitations, chest pain, or recurrent syncope, any of which should lead to a cardiac evaluation. The presence of a prolonged PR interval (most common) or other changes should result in an evaluation by a cardiologist, as these changes are progressive and may result in sudden death. These patients will require the placement of a pacemaker or implantable cardioverter-defibrillator.[53]

### Sleep and Pulmonary Management

Excessive daytime sleepiness affects the majority of patients with DM1 and is rated as the most impactful symptom of the disease. It is important to screen both patients with DM1 and patients with DM2 for the presence of central or obstructive sleep apnea. Patients should have a sleep study at baseline and when prompted by symptoms of excessive daytime sleepiness and should be counseled on appropriate sleep hygiene, including alcohol and caffeine consumption. Noninvasive positive pressure ventilation may be warranted when the sleep study demonstrates apnea. Stimulant therapy with either modafinil or armodafinil may be considered when the excessive daytime sleepiness impairs function.[56]

Respiratory function should be assessed in the upright and supine position. Patients with DM1 should be monitored on an annual basis. Early intervention with noninvasive positive pressure ventilation may be required. The frequency of respiratory failure in DM2 is thought to be lower than in DM1, although this has not been formally studied. In general, patients with DM2 should be monitored at diagnosis and when symptoms prompt additional evaluation. Additionally, patients with DM1 and DM2 should be counseled to receive vaccinations for influenza and pneumonia if no contraindications are present.

### Gastrointestinal System Management

Patients with DM1 may have dysfunction throughout the gastrointestinal tract. Patients should be screened for swallowing difficulties, with appropriate referral to a speech therapist for guidance on dietary modifications. Patients may require a nutrition consultation if their dysphagia causes weight loss. In addition, patients may have dysarthria that may benefit from periodic speech therapy or have gastroesophageal reflux that may benefit from standard therapies.

Patients with DM1 or DM2 may have intractable irritable bowel symptoms. Patients should be screened with a glucose breath test for a bacterial overgrowth syndrome and treated appropriately if the test is positive. A high-fiber diet is the first-line treatment for patients with diarrhea or constipation. Loperamide may be considered for diarrhea and gentle laxatives for constipation. If these treatments are ineffective, consider referral to a gastroenterologist.

### Ocular Management

Patients with DM1 or DM2 are at high risk of developing early-onset cataracts.[6] Therefore, an annual slit-lamp examination to screen for cataracts is recommended. Symptomatic cataracts should be removed as appropriate. Patients with DM1 often have ptosis, and, rarely, this can become severe enough to interfere with vision. In these cases, eyelid crutches may be warranted. Finally, eye closure weakness in DM1 may result in corneal abrasions. In patients who have eye closure weakness on examination, use of a lubricant eye ointment at night may be considered.

### Endocrine System Management

Patients with DM1 or DM2 require annual screening for thyroid deficiency. Thyroid hormone replacement should be considered as appropriate. Periodic screening for insulin resistance, hyperlipidemia, or testosterone deficiency (in men) is also recommended.

### Anesthesia

Patients with DM1 are at increased risk with administration of general anesthesia. Complications include a hypersensitivity to opiate medications and a paradoxical reaction to muscle-depolarizing agents. Risks also include postoperative apnea requiring a prolonged ventilator wean. While a single study did not identify complications in DM2, caution is still advised in these patients. The Myotonic Dystrophy Foundation provides guidelines for surgical anesthesia (*myotonic.org/mdf-releases-updated-anesthesia-guidelines*).

**KEY POINTS**

- Both patients with myotonic dystrophy type 1 and patients with myotonic dystrophy type 2 benefit from moderate-intensity aerobic exercise.
- Skeletal muscle myotonia in patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 may be treated with several different agents that target skeletal muscle sodium channels, such as mexiletine.
- Patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 are at an increased risk of developing life-threatening cardiac arrhythmias. It is recommended that patients have an ECG at diagnosis and annually thereafter.
- It is important to screen patients with myotonic dystrophy type 1 and patients with myotonic dystrophy type 2 for the presence of central or obstructive sleep apnea.
- Patients with myotonic dystrophy type 1 or myotonic dystrophy type 2 should be screened with a glucose breath test for a bacterial overgrowth syndrome and treated appropriately if the test is positive. A high-fiber diet is the first-line treatment for patients with diarrhea or constipation.
- Patients with myotonic dystrophy are at risk of thyroid deficiency, which may exacerbate their fatigue and myotonia without treatment.

### Pregnancy

Specific management issues in pregnant patients with myotonic dystrophy are worth noting. Patients with DM1 are at risk of increasing myotonia and weakness, among other disease manifestations, during pregnancy. Prior survey results suggest that these symptoms typically improve following delivery, although it is possible women may experience a permanent progression in their disease. Women with DM2 report increased pain and weakness during the course of pregnancy and were less likely to report a return to prior function following pregnancy. Women with DM1 or DM2 are at risk of a number of complications during pregnancy, including preeclampsia, prolonged labor, peripartum hemorrhage, and worsening of the symptoms of myotonia and fatigue during pregnancy.

### Monitoring for Neoplasms

While the increased risk of cancer is clearly identified in DM1 and DM2, the current recommendations remain to counsel patients to stay up-to-date on routine screenings for their age and sex. Clinicians should be aware of this risk so that new symptoms, such as profound weight loss, are given appropriate attention.

## FUTURE DIRECTIONS

Increased understanding of disease pathogenesis and novel disease-modifying technologies, such as antisense oligonucleotides and gene replacement therapies, have accelerated progress toward new treatments for myotonic dystrophy. Much of these efforts have occurred in DM1 because the pathogenesis has been better investigated and natural history studies designed to develop appropriate clinical outcome assessments for therapeutic trials are better developed. However, given the commonalities between DM1 and DM2, many in the field believe that therapies developed for DM1 will be readily transferable to DM2. Common approaches to developing disease-modifying therapies include small molecules designed to bind the GC-rich repeats to silence transcription, small molecules designed to disrupt the interaction between the CTG repeat and RNA-binding proteins such as MBNL1, and antisense oligonucleotides designed to bind the repeat and silence it. Other approaches modulate downstream effects as well, but the described approaches are the most likely to lead to disease modification.

To silence transcription, several investigators have identified small molecules that bind to the CTG repeat and reduce the expression of the toxic RNA product. These include compounds such as pentamidine and actinomycin D.[57,58] Unfortunately, these have, thus far, had toxicity in animal models at potentially efficacious doses in preclinical studies. Additional efforts are under way to identify similar compounds.

To prevent the interaction between the toxic CUG repeat and RNA-binding proteins, several groups have rationally designed therapeutics to bind to the CUG repeat and prevent binding of other proteins, such as the MBNL family.[59,60] In doing so, proteins such as MBNL1 are permitted to continue to regulate RNA alternative splicing. These types of therapies have the potential to cross the blood-brain barrier and are more likely to have tissue penetration in skeletal muscle, increasing the target engagement.

Finally, antisense oligonucleotides offer an approach to directly target the CUG repeat. The current approach uses an antisense oligonucleotide that targets

a sequence near the CUG repeat and promotes an RNase H1 activity to degrade the toxic transcript.[61] The approach is appealing given the precision of the therapy and high likelihood of modifying the disease. However, antisense oligonucleotide therapies are unable to cross the blood-brain barrier. Nonetheless, a phase 1/2a study using this approach was conducted in adults with DM1 (NCT02312011).[62] The results are still pending, but this appears to be a promising approach.

**KEY POINT**

- **Patients with myotonic dystrophy type 1 are at increased risk with use of general anesthesia. Complications include a hypersensitivity to opiate medications, a paradoxical reaction to muscle-depolarizing agents, or a prolonged ventilatory wean.**

## CONCLUSION

The myotonic dystrophies, the most common forms of muscular dystrophy, represent multisystem conditions that affect nearly every organ system in the body. Management of patients with these disorders requires a multidisciplinary team and a care management plan to focus on the diverse range of complications that may arise. Recent advances targeting the interaction between the toxic repeat and the RNA-binding proteins that are sequestered hold promise that these conditions will have additional treatments available in the future.

## USEFUL WEBSITES

**MYOTONIC DYSTROPHY FOUNDATION ANESTHESIA GUIDELINES**
The Myotonic Dystrophy Foundation provides guidelines that address the special risks in the use of anesthesia in patients with myotonic dystrophy.
*myotonic.org/mdf-releases-updated-anesthesia-guidelines*

**MYOTONIC DYSTROPHY FOUNDATION CLINICAL CARE RECOMMENDATIONS**
The Myotonic Dystrophy Foundation provides recommendations around the care of patients with myotonic dystrophy type 1 and type 2.
*myotonic.org/clinical-resources*

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