CURRENT OPINION

Myotonic dystrophy: diagnosis, management and new therapies

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Purpose of review
Myotonic dystrophies type 1 and type 2 are progressive multisystem genetic disorders with clinical and genetic features in common. Myotonic dystrophy type 1 is the most prevalent muscular dystrophy in adults and has a wide phenotypic spectrum. The average age of death in myotonic dystrophy type 1 is in the fifth decade. In comparison, myotonic dystrophy type 2 tends to cause a milder phenotype with later onset of symptoms and is less common than myotonic dystrophy type 1. Historically, patients with myotonic dystrophy type 1 have not received the medical and social input they need to maximize their quality and quantity of life. This review describes the improved understanding in the molecular and clinical features of myotonic dystrophy type 1 as well as the screening of clinical complications and their management. We will also discuss new potential genetic treatments.

Recent findings
An active approach to screening and management of myotonic dystrophies type 1 and type 2 requires a multidisciplinary medical, rehabilitative and social team. This process will probably improve morbidity and mortality for patients. Genetic treatments have been successfully used in in-vitro and animal models to reverse the physiological, histopathological and transcriptomic features.

Summary
Molecular therapeutics for myotonic dystrophy will probably bridge the translational gap between bench and bedside in the near future. There will still be a requirement for clinical screening of patients with myotonic dystrophy with proactive and systematic management of complications.

Keywords
CNBP, myotonic dystrophy protein kinase, myotonic dystrophy type 1, myotonic dystrophy type 2, proximal myotonic myopathy, Steinert's disease, ZNF9

INTRODUCTION

Myotonic dystrophies type 1 and type 2 are progressive multisystem autosomal dominant disorders because of unstable nucleotide repeat expansions in untranslated DNA. The mutation leads to mis-splicing of mRNA species which affects many cellular processes and has led to the formation of a novel group of diseases called the 'spliceopathies'. Myotonic dystrophies type 1 and type 2 share many clinical and genetic features. Myotonic dystrophy type 1 is the commonest muscular dystrophy in adults with a wide clinical phenotype ranging from the asymptomatic form to a severe, life-threatening, congenital disease. This is in comparison to myotonic dystrophy type 2 which is less common and associated with a milder phenotype. This review will focus on novel management strategies in adults, and potential treatments, in particular for myotonic dystrophy type 1, although their application is likely to be applicable to myotonic dystrophy type 2.

THE MOLECULAR BASIS OF MYOTONIC DYSTROPHIES TYPE 1 AND TYPE 2

Myotonic dystrophy type 1 is caused by the expansion of an unstable trinucleotide (CTG) repeat sequence in an untranslated, but transcribed, portion of the 3′ untranslated region of the myotonic dystrophy protein kinase (*DMPK*) gene located on chromosome 19q13.3 (Fig. 1) [1]. Normal individuals have between 5 and 37 CTG repeats. Patients with between 38 and 49 CTG repeats (the 'premutation allele') are asymptomatic but are at risk of

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KEY POINTS

- Myotonic dystrophy type 1 is the commonest muscular dystrophy in adults and is associated with early mortality, averaging 54 years.
- Myotonic dystrophy type 1 is a multisystem disease with 70% of early mortality caused by cardiorespiratory complications.
- Complications of myotonic dystrophy type 1 should be actively monitored and managed within a multidisciplinary team.
- Genetic treatments have been developed *in vitro* and in animal models. The early phases of human trials have begun.
- Myotonic dystrophy type 2 shares similar clinical and genetic features to myotonic dystrophy type 1 but is less common and is associated with a milder phenotype.

having children with larger repeats caused by intergenerational repeat expansion due to anticipation [2]. Fully penetrant alleles occur with greater than 50 CTG repeats. PCR is used to detect repeat lengths of less than 100 and Southern blot analysis to detect larger expansions, although increasingly triplet-primed PCR (TP-PCR) is utilized because this method has several advantages, including being less labour intensive and probably more sensitive [3], although it does not estimate the size of the repeat.

There is a moderate correlation between longer CTG repeat expansions and an earlier age of onset and more severe disease, especially below 400 CTG repeats [4]. One explanation for the limited correlation of phenotype with repeat size above 400 is that the DMPK CTG trinucleotide repeat length is unstable in individuals with myotonic dystrophy type 1, which leads to somatic mosaicism for the size of the CTG expansion [5]. The repeat size is stable in some postnatal tissues, for example leucocytes, but not in others, for example skeletal and cardiac muscle. The diagnostic test result from leucocyte DNA correlates poorly with expansion size in affected tissues and organs. Somatic instability occurs in mitotic and postmitotic tissues, suggesting that it is caused by changes in DNA repair mechanisms. The estimated progenitor allele length and level of somatic instability have recently been described as major modifiers of age of onset and support the hypothesis that the variation in disease severity between organs, within an individual, may partly be related to the level of somatic mosaicism within each organ [6▪▪].

There is increasing evidence that the transcribed mutant *DMPK* mRNA is directly toxic by affecting RNA splicing factors such as muscleblind-like splicing regulator 1 (MBNL-1) and CUG binding protein 1 (CUG-BP1) as well as more recently described Staufen 1 and DEAD box protein 5 (DDX5) [7,8]. This causes abnormal splicing of mRNA transcripts, such as the muscle chloride ion channel, resulting in myotonia [9], with novel mis-splicing events continually being described [10]. Abnormal mRNA splicing may occur because of the accumulation of splicing factors within ribonuclear accumulations of

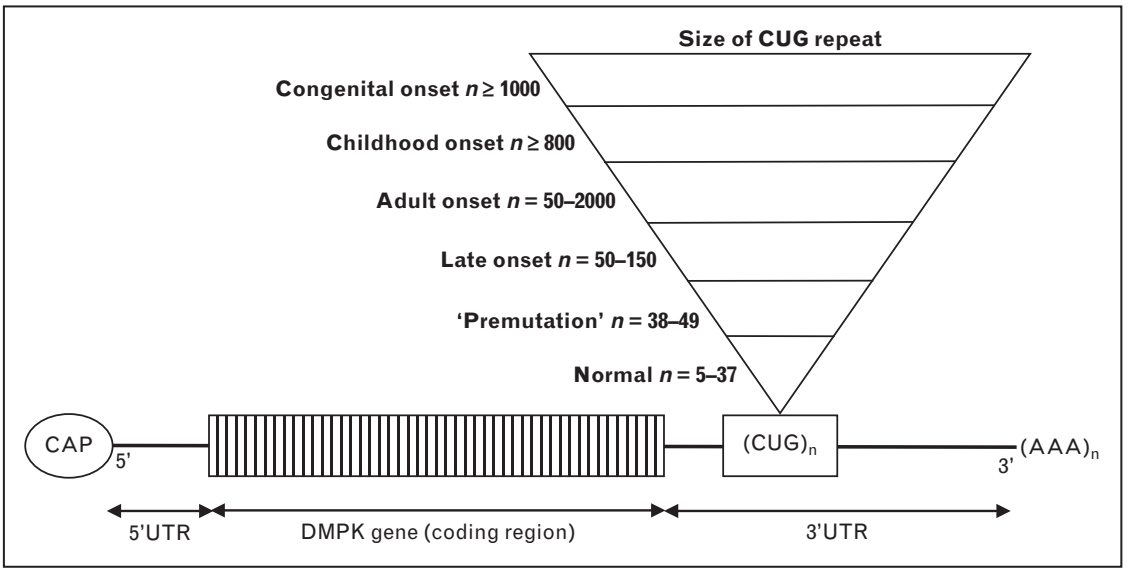

FIGURE 1. Myotonic dystrophy protein kinase mRNA with relationship between CUG repeat size and phenotype. There are five clinically defined forms of myotonic dystrophy type 1 based on the age of onset and CTG repeat size. The mutation lies within the 3′ UTR of the *DMPK* gene and is shown within the *DMPK* mRNA. This molecule aggregates to form a ribonuclear inclusion. UTR, untranslated region; DMPK, myotonic dystrophy protein kinase. Source: Original.

mutant *DMPK*, affecting splicing factors within the nucleus independent of the ribonuclear inclusions [11]. The molecular pathophysiology may be even more complex than previously thought, and recently bidirectional antisense transcription, dysregulation of microRNAs and potentially non-ATG-mediated translation of homopolymeric toxic proteins have been described as novel mechanisms of RNA toxicity [12▪▪].

Myotonic dystrophy type 2 is caused by expansion of a complex repeat motif (TG)n(TCTG)n (CCTG)n in the first intron of the *CNBP* (cellular nucleic acid-binding protein; previously 'ZNF 9', zinc finger protein 9) gene [13]. A similar molecular mechanism of widespread cellular abnormalities of mRNA splicing has also been proposed for myotonic dystrophy type 2.

CLINICAL FEATURES AND MANAGEMENT IN ADULTS WITH MYOTONIC DYSTROPHY TYPE 1

Myotonic dystrophy type 1 has a prevalence of between 3 and 15 per 100 000 [14], although this is higher in specific regions such as Quebec, where the incidence rises to 1 in 500 [15]. Patients with myotonic dystrophy type 1 can be clinically divided into five main subtypes based on the age at presentation (Table 1). This review will focus on adult onset myotonic dystrophy type 1 which is the commonest form and details of the other forms can be found in recent reviews [16,17]. The 'classical' or adult-onset form of myotonic dystrophy type 1 may affect virtually any organ and the most severely involved shall be discussed.

SKELETAL MUSCLE

Skeletal muscle involvement is characterized by a dystrophic process, causing weakness, and by a defect in muscle membrane excitability causing myotonia. Symptomatic grip myotonia often precedes any symptoms of weakness. A highly characteristic pattern of facial weakness with ptosis, atrophy of temporalis and premature hair loss, particularly in men, causes the typical facial appearance. Neck weakness, particularly flexion, is common but a 'dropped head' may also occur with extensor weakness. The long finger flexors are affected early and cause disabling and prominent functional problems. Weakness of ankle dorsiflexion is common and is one of the main mechanisms that cause falls. Muscle weakness progresses slowly over several years, but substantial proximal weakness is a late feature. Dehydroepiandrosterone (DHEA) [18], recombinant insulin-like growth factor 1 (IGF-1) and its binding protein, BP-3 (rhIGF-1/rhIGFBP-3) [19], and creatine [20–22] have not been found to have consistent benefits in improving muscle power. Routine use of these agents cannot be recommended on current evidence. Moderate-intensity strength training appears not to cause harm in myotonic dystrophy type 1 [23], and in spite of the lack of evidence of benefit, we strongly recommend that all patients undertake regular exercise which we believe is likely to help with muscle strength and stamina, general cardiovascular fitness and weight control.

Myotonia may also affect the face, jaw, tongue and swallowing. Myotonia may improve with repeated contractions, and this is called the 'warm-up phenomenon' [24]. Many drugs have been given for the treatment of myotonia and have been the subject of a Cochrane review [25]. There are theoretical concerns about the potential cardiac side-effects of the antimyotonia drugs; however, mexiletine at doses up to 200 mg three times a day have been found to be effective and well tolerated [26].

HEART

Conduction disturbances and tachyarrhythmias are common in myotonic dystrophy type 1 [27–29]. In

Table 1. A summary of the clinical phenotype and CTG repeat length in myotonic dystrophy type 1

Phenotype	Clinical signs	CTG repeat size	Age of onset/years	Age of death/years
Premutation	None	38–49	N/A	N/A
Mild	Cataracts, mild myotonia	50–150	20–70	Normal life span
Classical	Muscle weakness with respiratory failure, myotonia, cataracts, cardiac arrhythmias, EDS	50–1000	10–30	48–60
Childhood onset	Psychosocial problems, low IQ, incontinence	>800	1–10	N/A
Congenital	Infantile hypotonia, respiratory failure, learning disability, feeding difficulty	>1000	Birth	45 (neonatal deaths not included)

This table demonstrates the correlation between type of myotonic dystrophy type 1, clinical features, CTG repeat size, age of onset and death. The correlation of age of onset with CTG repeat size is modest when the expansion size is measured in leucocyte DNA. EDS, excessive daytime sleepiness; IQ, intelligence quotient, N/A, not available.

study [30], mean age of death was 53 years. There was a positive correlation between age of onset and age at death with 30% of the deaths due to cardiac complications. The cardiac abnormalities included sudden unexpected death, presumed to be due to a malignant arrhythmia, progressive left ventricle dysfunction and ischaemic heart disease, although there is no conclusive evidence of early atherosclerosis in myotonic dystrophy type 1. A study investigating sudden death in patients with myotonic dystrophy type 1 found that a severe abnormality on the ECG (defined as a prolonged PR and/or QRS interval, second/third-degree heart block or a nonsinus rhythm) or a diagnosis of an atrial tachyarrhythmia predicted sudden death [31]. Over a 5.7-year follow-up, 7% of patients experienced sudden death and 8% died from respiratory failure. In contrast to cardiac arrhythmias, cardiomyopathy is rarely a significant feature.

We recommend yearly ECG, with a low threshold for cardiology referral if there is marked prolongation of the PR interval or QRS complex, any form of conduction block or if the patient develops cardiac symptoms. A significant bradyarrhythmia can be treated with insertion of a permanent pacemaker. Eighteen per cent of patients with a normal 24-h Holter monitor have inducible ventricular tachyarrhythmias in the absence of symptoms on electrophysiological studies [32]. The criteria for inducible ventricular tachyarrhythmias and its relevance remain debated. It is not certain how many of these patients develop dangerous arrhythmias and would benefit from insertion of an implantable cardioverter defibrillator. An 'invasive strategy', consisting of electrophysiological cardiac studies, has been found to be associated with a higher rate of 9-year survival than a 'noninvasive strategy' [33▪]. However, the study was retrospective and required statistical correction for bias in the entry into the two groups. The development of smaller and safer implantable cardiac devices to monitor heart rhythms may provide sufficient data to determine patients at risk of serious cardiac complications.

RESPIRATORY FUNCTION AND DAYTIME SLEEPINESS

Excessive daytime sleepiness (EDS) and respiratory failure are very common in myotonic dystrophy type 1. EDS and respiratory failure tend to occur independently of one another [34] and often significantly reduce quality of life. Respiratory failure, usually in the context of aspiration pneumonia, causes at least 40% of all case early mortality in myotonic dystrophy type 1 [30]. Respiratory failure is caused by respiratory muscle (especially diaphragmatic) weakness, which can manifest as a poor cough and reduced vital capacity [35]. General anaesthesia often precipitates respiratory failure in patients who were previously clinically stable. A 10% risk of postoperative complications due to general anaesthesia including prolonged respiratory depression from anaesthetic agents and postoperative pneumonia, especially following cholecystectomy, highlights the need for careful perioperative management of patients with myotonic dystrophy [36]. Regular screening should include annual assessment of vital capacity; overnight sleep oximetry is indicated if there are symptoms suggesting sleep disturbance or EDS and if the vital capacity is less than 1.5 l. If there is objective evidence of sleep apnoea, patients should be offered noninvasive ventilation (NIV), although many patients do not tolerate nocturnal NIV for reasons that have not been fully elucidated.

EDS is present to varying degrees in at least 39% of patients with myotonic dystrophy type 1 [37,14] and often has a major impact on quality of life for the patient and their family. EDS is infrequently due to sleep-disordered breathing and appears to originate from primary central nervous system dysfunction [38–40]. EDS often responds to the psychostimulant drug modafinil, although the literature is contradictory. Three cross-over studies [41–43] and one open-label study [44] found benefit. A Cochrane review [45] of psychostimulants in myotonic dystrophy type 1 suggested that further trials were needed. Recent patient-centred observations provide strong support for a trial of modafinil in appropriately assessed patients [46▪]. We would recommend modafinil at 200 mg in the morning, increased after 2 weeks to 200 mg in the morning and at lunchtime if there was no response at the lower dose. If there is still no clear benefit, then the drug should be stopped.

NEUROLOGICAL AND PSYCHIATRIC DISTURBANCE

Specific cognitive and intellectual deficits are frequent in adult myotonic dystrophy type 1 but substantially milder and less of a clinical issue than in those with congenital and childhood myotonic dystrophy type 1. Patients uncommonly develop overt 'dementia'. Age-related cognitive decline has been reported in adults [47–50], but in clinical practice, any such changes are less striking than the physical progression of the disorder. Abnormal personality features have been described [51–53]. A broad range of neuropsychological defects in frontal, parietal

and temporal lobe functions have been described, although frontal lobe involvement predominates and deficits in recognition of facial emotion, similar to patients with schizophrenia, suggest a possible similar pathophysiology [53–56]. White matter lesions and loss of specific regions of grey matter have been described on MRI [55–57]. The cognitive phenotype remains complex and relatively uncharacterized and has a significant impact on the function and quality of life of the patient and relatives.

Neurons in the limbic system and brainstem contain tau-associated neurofibrillary tangles in myotonic dystrophies type 1 and type 2, suggesting a common neuropathological process and a possible link with the central nervous system features of myotonic dystrophy type 1, including apathy and sleepiness [58,59]. A unique abnormal pattern of tau isoform expression in myotonic dystrophy type 1 and transgenic mice has been described. This consists of reduced exon 2/3-containing isoforms, hyperphosphorylated tau and a predominance of shorter tau isoforms including exon 10 only or no additional exons [60,61].

GASTROINTESTINAL DYSFUNCTION

Prospective studies of gastrointestinal symptoms in myotonic dystrophy type 1 patients have found that abdominal pain (55%), dysphagia (45%), emesis (35%), chronic or episodic diarrhoea (33%), coughing while eating (33%) and anal incontinence (30%) are common symptoms [62,63]. The commonest gastrointestinal symptom complex is similar to irritable bowel syndrome. The burden for patients of gastrointestinal-related symptoms has generally been under-recognized [62,63]. Liver function tests are often elevated for unknown reasons [64]. Many patients will not complain of problems with swallowing even when there is significant aspiration on videofluoroscopy. We would therefore recommend speech therapy assessment in patients with recurrent chest infection and prominent coughing on eating or drinking. Some patients require intervention such as oesophageal balloon dilatation, cricopharyngeal myotomy and, rarely, percutaneous endoscopic gastrostomy (PEG), although PEG insertion probably should be discussed as a therapeutic option more often and earlier than currently practised. Cholestyramine may improve diarrhoea, incontinence and pain, possibly by preventing large-bowel osmotic diarrhoea due to failure of absorption of bile salts in the terminal ileum. Norfloxacin, other quinolones and doxycycline may be effective when cholestyramine fails by treating bacterial overgrowth, and erythromycin or domperidone may help to improve gastric emptying by compensating for reduced motilin levels in myotonic dystrophy type 1 [62,63].

ENDOCRINE DYSFUNCTION

Endocrine abnormalities include disturbances of the thyroid, pancreas, hypothalamus, gonads and, more recently identified, parathyroids [65]. Testicular atrophy, with atrophy of the seminiferous tubules, leads to infertility in men. Infertility may occur in otherwise asymptomatic patients [66]. In women, habitual abortion and menstrual irregularities are common. Diabetes mellitus is probably slightly common in myotonic dystrophy type 1 than in the general population; however, hyperinsulinemia, due to insulin resistance secondary to abnormal splicing of the insulin receptor mRNA to a more insulin-insensitive isoform, has long been recognized [67–69]. Obesity in inactive individuals increases the risk of diabetes. Attention should be paid to symptoms of diabetes, of which the patient should be informed, but annual fasting blood glucose estimation is practically very difficult. Given recent revised guidelines, annual glycated haemoglobin (HbA1c) estimation may be appropriate [70].

PREGNANCY

Women with myotonic dystrophy type 1 are at risk of complications during pregnancy, including an increased rate of spontaneous abortion, prolonged labour, retained placenta and postpartum haemorrhage [71,72]. Most women can expect to have a normal vaginal delivery and the greatest obstetric or neonatal issues are seen when a congenitally affected child is born. Prenatal diagnosis (via chorionic villus sampling) gives the option of selective termination of pregnancy. An increasingly available option is preimplantation genetic diagnosis [73].

MYOTONIC DYSTROPHY TYPE 2

Myotonic dystrophy type 2 shares many of the multisystemic features of myotonic dystrophy type 1 [74–77]. The onset of myotonic dystrophy type 2 is typically in the third decade, but often much later, with the most common presenting symptom being mild muscle weakness [76,77]. Myotonic dystrophy type 2 patients much more commonly have prominent muscle pain, stiffness and fatigue compared with myotonic dystrophy type 1, although muscle pain may be underestimated in myotonic dystrophy type 1. The weakness typically affects proximal muscles and often is mild [77]. Cardiac conduction defects, cataracts and insulin insensitivity are common. Cognitive manifestations in myotonic

Table 2. A proposed system for monitoring the multisystem involvement in myotonic dystrophies type 1 and type 2

System	Monitor	Treatment
Cardiac	Yearly ECG. Consider ECHO/24hr Holter/EPS if indicated.	PPM/ICD Medical treatment of AF
Respiratory	Yearly VC. Sleep study if indicate Frequency of antibiotics and chest infections	Noninvasive ventilation
EDS	ESS or equivalent	Psychostimulants including modafinil
Gastrointestinal	Swallowing difficulties Postprandial vomiting/bloating/nausea IBS-type symptoms Weight loss	Consider domperidone or erythromycin Consider cholecystyramine, quinilone, doxycycline SALT and Dietetic review PEG
Muscle weakness	Foot drop, finger grip, head drop, ptosis, falls	Orthotics/physiotherapy/OT/social services/eyelid surgery
Myotonia	Hand grip, speech/swallowing, myalgia	Consider mexiletine
Eyes	Cataracts	Surgery
Endocrine	Symptoms suggestive of diabetes. Fasting blood glucose, or HbA1c estimation, TFTs, calcium/vitamin D, fertility	Hypoglycaemics/insulin, thyroxine, vitamin D supplementation, fertility clinic
Bladder	Incontinence, frequency and urgency (especially in women)	Uro-neurology/urology referral
Skin	Monitor for pilomatrixomas Male pattern balding	Surgery Consider minoxidil or finasteride cream
Patient support	Check patients and carers understanding Check medic alert bracelet/necklace Check carrying care card	Provide details of regional and national groups Contact with nurse specialist or similar In the UK, Myotonic Dystrophy Support Group (MDSG) (http://www.myotonicdystrophysupportgroup.org/) and the Muscular Dystrophy Campaign (MDC) (http://www.muscular-dystrophy.org/).
Diagnosis and pregnancy	Counselling	Genetic testing PGD Antenatal screening

A proactive, multidisciplinary approach is recommended to the monitoring of the complications of myotonic dystrophies type 1 and type 2. AF, atrial fibrillation; ECHO, echocardiogram; EDS, excessive daytime sleepiness; EPS, electrophysiological studies; IBS, irritable bowel syndrome; ICD, implantable cardioverter defibrillator; OT, occupational therapy; PEG, percutaneous endoscopic gastrostomy; PGD, pre-implantation genetic diagnosis; PPM, permanent pacemaker; TFT, thyroid function test; VC, vital capacity. Source: Original.

dystrophy type 2 are less severe than in myotonic dystrophy type 1. As a precaution, we apply similar screening protocols to myotonic dystrophy type 2 patients, although the natural history is less clearly defined than in myotonic dystrophy type 1.

SCREENING IN MYOTONIC DYSTROPHY

There is currently no cure for myotonic dystrophy. Cardiorespiratory disorders are responsible for 70% of mortality in myotonic dystrophy type 1 and there is good evidence that active monitoring and timely intervention significantly reduce morbidity and mortality. A summary of our optimized screening protocol can be found in Table 2.

A strategy for managing patients and developing a Standards of Care protocol has been described [78,79].

GENE THERAPY

The recent advances in our understanding of the underlying molecular mechanisms involved in myotonic dystrophy have generated new approaches for more specific and effective treatments for myotonic dystrophies type 1 and type 2. The development of targeted molecular treatments, especially antisense oligonucleotide (ASO) therapy, has achieved success *in vitro* and in animal models, although the translation of this to human trials has lagged behind because of difficulties in targeting affected tissues with a nontoxic dose [80]. There are examples of recent studies which have provided cause for optimism in bridging the translational gap. In a transgenic mouse model of myotonic dystrophy type 1, systemic administration of ASOs caused a rapid knockdown of CUG(exp) RNA in skeletal muscle, correcting the physiological, histopathological and transcriptomic features of the disease for up to 1 year after the treatments were stopped [81▪▪]. A practical application of RNA technology has been applied to myotonic dystrophy type 1 tibialis anterior muscle in which 20 RNA splicing biomarkers demonstrated graded changes that correlated with ankle dorsiflexion (ADF) weakness. Five other splice events were strongly affected in myotonic dystrophy type 1 patients with normal ADF power, suggesting that presymptomatic changes can be detected and

potentially used to determine the timing of potentially toxic treatments [82▪▪].

CONCLUSION

Myotonic dystrophy type 1 is the most prevalent muscular dystrophy and is associated with high levels of morbidity and premature mortality. There is currently no cure, but proactive management is likely to significantly reduce morbidity and mortality in a patient population who have often received little medical input beyond diagnosis. The rapid advances in the understanding of the molecular pathogenesis have placed the myotonic dystrophies at the vanguard of modern genetic treatments, which has already achieved significant disease-modifying effects *in vitro* and in animal models. The dawn of gene therapy for myotonic dystrophies type 1 and type 2 appears to be very close, and the near future is an exciting time for clinicians and patients alike.

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Conflicts of interest

CT and DHJ have no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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