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Review

Expert opinion on mexiletine treatment in adult patients with myotonic dystrophy☆

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ABSTRACT

In France, mexiletine – a class I antiarrhythmic drug – can be prescribed for the symptomatic treatment of myotonia of the skeletal muscles in adult patients with myotonic dystrophy under a compassionate use programme. Mexiletine is used according to its summary of product characteristics, which describes its use for myotonia treatment in adult patients with non-dystrophic myotonia, a different neuromuscular condition without cardiac involvement. A cardiac assessment is required prior to initiation and throughout treatment due to potential proarrhythmic effects. The presence of conduction system disease, the most common cardiac manifestation of myotonic dystrophy, mandates repeated cardiac evaluations in patients with this condition, and becomes even more important when they are given mexiletine. A group of experts, including three neurologists and five cardiologists from French neuromuscular reference centres, were involved in a task force to develop a treatment algorithm to guide mexiletine use in myotonic dystrophy. The recommendations are based on data from a literature review of the safety of mexiletine-treated patients with myotonic dystrophy, the compassionate use protocol for mexiletine and the personal clinical experience of the experts. The main conclusion of the expert group is that, although existing safety data in mexiletine-treated patients with myotonic dystrophy are reassuring, cardiac assessments should be reinforced in such patients compared with mexiletine-treated patients with non-dystrophic myotonia. This expert opinion to guide mexiletine treatment in patients with myotonic dystrophy should help to reduce the risk of severe adverse events and facilitate interactions between specialists involved in the routine care of patients with myotonic dystrophy.

☆ Tweet: A group of French cardiology and neuromuscular experts has established a new opinion document to improve the safety of mexiletine treatment for myotonia in adult patients with myotonic dystrophy, with a very practical algorithm on pre-treatment assessments and follow-up strategy.

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1. Abbreviations

AVB	atrioventricular block
CDM1	congenital dystrophic myotonia 1
DM	myotonic dystrophy
DM1	myotonic dystrophy type 1
DM2	myotonic dystrophy type 2
ESC	European Society of Cardiology

2. Background

Myotonic dystrophies (DMs) are complex multisystemic disorders linked to two different genetic loci: DM type 1 (DM1; Online Mendelian Inheritance in Man 160900, also known as Steinert's disease); and DM type 2 (DM2; Online Mendelian Inheritance in Man 602668). DMs are the most common muscular dystrophies in adults, with an estimated combined prevalence of 1 per 8000 individuals [1]. A recent population-based study suggested that the prevalence of DM1 could be fourfold higher (4.8 per 10,000) and that DM1 could be highly underdiagnosed in practice [2]. DM is primarily characterized by myotonia, skeletal muscle weakness and wasting and progressive myopathy [3]. Patients experience highly variable multisystemic symptoms affecting the brain, heart, skeletal muscle, reproductive system and gastrointestinal tract [4].

It has been estimated that cardiac abnormalities can affect more than half of patients with DM [5]. DMs are associated with an increased risk of atrial arrhythmias, conduction system disease, ventricular arrhythmias and dilated cardiomyopathy [5]. The main pathophysiological mechanism underlying cardiac manifestations of DM is cardiac sodium channel dysfunction secondary to *SCN5A* gene mis-splicing [5]. Several international recommendations and expert consensus documents for the cardiac management of patients with DM1 and DM2 have recommended a 12-lead electrocardiogram upon diagnosis [5–9] and possibly a 24-hour Holter electrocardiogram and an electrophysiological study in patients with evidence of conduction system disease [7–9]. Regarding the possible progression of cardiac abnormalities, cardiac evaluation of patients with DM should be repeated during follow-up [5].

Currently, there is no disease-modifying therapy available for patients with DM in a routine care setting, although several candidates that aim to relieve myotonic symptoms are currently under investigation [10]. Mexiletine, although an antiarrhythmic agent, has been prescribed in myotonic disorders for over 30 years [11]. According to the Vaughan-Williams classification, mexiletine is a class I antiarrhythmic drug (i.e. it acts as a voltage-gated sodium channel blocker) [12]. Mexiletine has been repurposed to attenuate myotonia in patients with DM and non-dystrophic myotonic disorders, and its marketing authorization in Europe targets mexiletine access to adult patients with non-dystrophic myotonia [13]. In France, a compassionate programme based on the recommendations in the summary of product characteristics of mexiletine (NaMuscla; Lupin Europe GmbH, Frankfurt am Main, Germany) extends the therapeutic indication to adult patients with DM [14]. In this setting, mexiletine must be prescribed following marketing authorization rules, by a physician in a public hospital, who explains the benefits and risks of the treatment to patients and the specific scope of its compassionate usage. The physician must also deliver two documents to the patient to provide specific information on the mexiletine compassionate programme and the management of severe adverse events, including cardiac complications. Following this first visit, patients will attend appointments after 1, 2 and 4 weeks to monitor the efficacy and tolerance of the treatment and determine its optimal daily dose. However, this programme does not cover the different clinical cardiac conditions of the patients, for which detailed recommendations would be useful for practitioners.

Concerns have been raised regarding the use of mexiletine in patients with DM in relation to: (1) the high prevalence of arrhythmia manifestations in patients with this condition; (2) the cardiac pathomechanisms of DM involving sodium current dysfunction; and (3) the potential ventricular proarrhythmic effect of class I antiarrhythmic drugs in patients with ischaemic cardiomyopathy or heart failure. The aim of this work was to provide expert opinion on the use of mexiletine in patients with DM, to assist physicians when prescribing mexiletine to such patients so that they can make informed decisions before treatment initiation and during the course of treatment. The algorithms resulting from this work are aimed at neurologists who follow up patients with DM and referring cardiologists who perform the cardiac assessments.

3. Myotonic dystrophies

The two genetically different types of DM – DM1 and DM2 – are both autosomal dominant multisystemic diseases that involve multiple organs (e.g. skeletal muscle, heart, brain and endocrine system). DMs are caused by unstable CTG expansions (from 37 to up to several thousand repeats) in the 3′ untranslated regions of the dystrophia myotonica protein kinase (*DMPK*) gene for DM1 [15], and CCTG expansions in the first intron of the cellular nucleic acid-binding protein (*CNBP*), previously known as zinc finger protein 9 (*ZNF9*) gene, for DM2 [16].

DM1 has five clinical forms: congenital DM1 (CDM1); childhood-onset DM1 or infantile form, with a clinical onset from age 1 month to 10 years; juvenile form (onset at age 11–20 years); classical adult form (21–40 years); and late-onset DM1 (> 40 years) [17,18].

Classical adult DM1 is characterized by myotonia, skeletal muscle weakness and wasting and progressive myopathy [19]. Muscle weakness develops in facial, neck and distal limb muscles in parallel with muscle wasting. Ptosis, along with atrophy and muscle weakness of temporal and mandibular muscles, give a characteristic myopathic facial appearance, which is a key feature of the disease. Myotonia is a core feature of DM1 on both clinical examination and electromyography. The most common sign is percussion myotonia in the thenar muscle and, less consistently, grip myotonia on activation [20]. The prevalence of myotonia in patients with DM1 has been estimated at 88% in the population aged 2–81 years [3]. Another study conducted in adult DM1 and DM2 showed severe myotonia (defined as time to open hands after contraction $\geq$ 3 seconds) in 30% of women and 44% of men [18]. In DM1, myotonia is more intense after rest and improves upon physical activity, often known as the "warm-up phenomenon". Later on, patients can develop cataracts and cognitive impairments (including attention, executive, memory and visuospatial defects) and a predisposition to type 2 diabetes.

CDM1, the most severe form of DM1, can affect development and survival. Surviving infants with CDM1 display learning disabilities and delays in cognitive and motor milestones; they can also develop other features seen in classic DM1 later in life, including myotonia, which affected such patients in a North American study with a prevalence of 69% [3]. Myotonia is usually the first manifestation of the disease, and affects each form of DM1. The probability of developing severe myotonia is higher in the juvenile form, affecting 44.3% of patients [19].

The childhood-onset and juvenile forms of DM1 are often underdiagnosed. Children usually present with difficulties at school that generally initiate an assessment by paediatric neurologists for causes of mental retardation. As with CDM1, most of the children develop myotonia and muscle weakness at an older age [21]. Late-onset DM1 is associated with cataracts, mild weakness and myotonia in patients aged > 40 years [22].

The two major causes of death in patients with DM1 are respiratory failure, due to progressive muscular weakness, and sudden death, which is mainly related to major cardiac conduction defects [23]. The annual incidence of sudden death in patients with DM1 and DM2 is 0.53–1.16% [24,25]. It has been estimated that one third of sudden deaths are related to atrioventricular conduction disturbances and ventricular arrhythmias, although catastrophic non-arrhythmic causes may also be implicated [9]. Cardiac complications include different supraventricular and ventricular tachyarrhythmias and various degrees of atrioventricular block (AVB) and bundle branch block, which are consequences of myocardial fibrosis and degeneration of the cardiac conduction system. Intraventricular conduction defects commonly occur through various mechanisms, which affect 30–70% of patients with DM1 [26]. Furthermore, patients with DM1 can also display cardiac pump malfunction with a reduced ejection fraction (< 40%) [5–8]. This led the American Heart Association [5], the European Society of Cardiology (ESC) [6] and the Heart Rhythm Society [9] to issue recommendations on the general cardiac evaluation or follow-up of such patients. Recommendations include performance of a 12-lead electrocardiogram in all patients upon confirmation of DM diagnosis [5–9]. Regular monitoring mainly includes surface 12-lead electrocardiograms, Holter electrocardiograms and echocardiograms [5,6]. Echocardiogram and Holter electrocardiogram monitoring are useful for the diagnosis of left ventricular systolic dysfunction, paroxysmal supraventricular and ventricular arrhythmias and paroxysmal advanced AVB. Echocardiogram and Holter electrocardiogram monitoring are generally reserved for patients with symptoms or evidence of conduction system disease. However, even in the absence of conduction system disease during initial screening, subsequent repeated evaluations can be indicated in asymptomatic patients (e.g. for patients aged > 40 years) [9].

Invasive electrophysiological testing is generally used when arrhythmic risk is not fully assessed by non-invasive studies or when a high index of suspicion of elevated arrhythmic risk persists despite normal or minimally abnormal findings. Whereas patients with PR interval ≥ 240 ms or QRS duration ≥ 120 ms are at higher risk of sudden death, the risk carried by patients with evidence of mild-to-moderate atrioventricular conduction impairment (e.g. PR interval 200–240 ms and/or QRS duration 100–120 ms), especially if coupled with symptoms suggestive of bradycardia, is uncertain [9].

DM2, which was originally called proximal myotonic myopathy, has significant clinical overlaps with DM1, but tends to have a milder phenotype. DM2 typically presents in adulthood, and the main difference between DM2 and DM1 is the absence of a congenital form. DM2 can be harder to recognize than DM1. Patients with DM2 present with prominent involvement of the proximal muscles, unlike patients with DM1 who present muscle weakness more marked in distal limb muscles. Facial weakness is mild, but calf muscle hypertrophy may be prominent. Skeletal muscle pain is a very common feature of the DM2 phenotype, as well as a highly relevant problem. Myotonia may be subtle clinically and only be present on electromyography. Myotonia affected 81% of the patients with DM2 in the North American study [3]. Like DM1, DM2 is associated with an increased risk of atrial arrhythmias, delays in conduction, ventricular arrhythmias, cardiomyopathy and heart failure, but these complications are much less common than in DM1 [22,27]. In a study of 104 patients with DM2 and 117 with DM1, the frequency and severity of cardiac involvement and muscle weakness were reduced in patients with DM2, and progression was slower and less severe [28]. However, recommendations for cardiac management in patients with DM2 are identical to those in patients with DM1 [5,6,8,9]. Patients with DM2 also develop a predisposition to type 2 diabetes, cataracts and abnormalities of the central nervous system, including mild brain atrophy [27].

As no disease-modifying therapy for any type of DM is available, current management is based on genetic counselling, preserving function and independence, preventing cardiopulmonary complications and providing symptomatic treatments for myotonia, hypersomnolence and pain [7,8]. Symptomatic treatments involve drug repurposing. Specific modifying therapies, such as oligonucleotide- and gene therapy-based approaches. are currently under investigation [10]. For the treatment of myotonia, mexiletine – which has an indication extension that covers adult patients with DM in France – is used routinely.

4. Mexiletine

Mexiletine – 1-(2′,6′-dimethylphenoxy)-2-aminopropane – is a primary amine with close structural similarities to lidocaine; it has local anaesthetic, anticonvulsant, antiarrhythmic and antimyotonic properties. Originally developed as an anticonvulsant drug, mexiletine, a class Ib antiarrhythmic agent according to the Vaughan-Williams classification, has been used for more than 45 years by cardiologists to treat cardiac arrhythmias [29,30]. Class Ib antiarrhythmics are prescribed to treat patients with ventricular tachycardia and long QT syndrome [12]. Congenital long QT syndrome comprises a distinct group of cardiac channelopathies characterized by QT prolongation on electrocardiogram and increased risk of syncope, seizures and sudden cardiac death. The 2022 ESC guidelines recommend the use of mexiletine in patients with long QT syndrome type 3 with a prolonged QT interval [6]. Indeed, mexiletine has been shown to reduce the length of the QT interval, as well as the number of arrhythmic events, with differences in responses to mexiletine depending on the mutations in the *SCN5A* gene that encodes the α subunit of the Nav1.5 channel [31].

Class I agents target the voltage-gated cardiac sodium channel Nav1.5, and class Ib drugs preferentially inhibit the late component of the sodium current (I_{Na}). Consequently, these drugs shorten action potential duration and prolong the effective refractory period, thereby reducing the risk of arrhythmia. These drugs display high variability in efficacy, and may have a proarrhythmic effect in some patients [12]. The Cardiac Arrhythmia Suppression Trial showed that patients treated with encainide or flecainide, two class Ic drugs, experienced more adverse events (including deaths due to arrhythmia) than patients in the placebo group [32]. The increased mortality was further confirmed by a meta-analysis of quinidine, a class Ia agent [33]. This increase in sudden deaths was thus extrapolated to all class I agents, including mexiletine.

The co-administration of several treatments with mexiletine is contraindicated or may require careful monitoring. Drugs that induce torsades de pointes, such as class Ia, class Ic and some class III antiarrhythmics, should be avoided, as mentioned in the summary of product characteristics, even though published data supporting such a risk are limited. It is noteworthy that these treatments are generally used for the treatment of cardiac arrhythmias, which themselves represent contraindications to mexiletine in patients with DM. Monitoring of mexiletine plasma concentration and dose adjustment may be required for patients treated with inducers of liver metabolism, including rifampin, phenytoin and phenobarbital, which may reduce the mexiletine plasma concentration [34]. Mexiletine, as an inhibitor of the CYP1A2 enzyme, can reduce the clearance of several drugs, such as duloxetine and paroxetine, whose co-administration is contraindicated, or theophylline, whose plasma concentration has to be monitored to avoid toxicity.

Mexiletine was approved by the European Medicines Agency in 2018 for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonia [13]. Myotonic syndromes are characterized by impaired muscle relaxation due to hyperexcitability

Table 1
Cardiovascular risks in mexiletine-treated patients with myotonic dystrophy.

	Study period	Patients	Study design	Dose	Treatment duration	Cardiovascular events (authors' comment)	Comments on inclusion criteria
Logigian et al. [41]	2000–2002	20 DM1	Randomized, double-blind, placebo-controlled, crossover trial	150 mg t.i.d.	7 weeks	No electrocardiogram or symptomatic abnormalities	Patients with first-degree AVB were included
Logigian et al. [41]	2001–2003	20 DM1	Randomized, double-blind, placebo-controlled, crossover trial	200 mg t.i.d.	7 weeks	No electrocardiogram or symptomatic abnormalities	Patients with first-degree AVB were included
Heatwole et al. [42]	2011–2017	42 DM1 with grip myotonia (21 mexiletine)	Randomized, double-blind, placebo-controlled trial	150 mg t.i.d.	6 months	No effect on cardiac conduction in treated patients	First-degree heart block and cardiac arrythmias treated with pacemaker included
Mousele et al. [43]	–	20 DM1; 5 DM2	Retrospective	Maximum 600 mg daily	Mean (range): 32.9 (0.1–216) months	No clinically relevant cardiac adverse events	11 patients with DM1 had cardiac morbidity before treatment with mexiletine
Vio et al. [35]	2011–2020	86 genetically confirmed DM1 (18 mexiletine)	Retrospective, longitudinal, comparative	200 mg b.i.d.	9 years	Risk of significant electrocardiogram modification and bradyarrhythmia complications was similar to that of non-treated patients	Mild cardiac conduction delay was included (28% in mexiletine cohort, 29% in non-mexiletine cohort)
Salguero-Bodes [44]	2000–2020	16 DM1	Retrospective review of the use of mexiletine as a drug authorized for "compassionate use"	200–600 mg	2–181 months	No significant cardiovascular events	–

AVB: atrioventricular block; b.i.d.: bis in die (twice daily); DM1: myotonic dystrophy type 1; DM2: myotonic dystrophy type 2; t.i.d.: ter in die (3 times daily).

of the muscle fibre membrane, and mexiletine non-selectively blocks sodium channels to restore a physiological activity close to normal. Mexiletine targets muscle sodium channel Nav1.4 involved in the hyperexcitability of the muscle fibre membrane. The inhibitory capacity of mexiletine is increased in situations of bursting action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurs in muscles affected by myotonia, rather than physiological excitability (resting or tonic block) [34,35]. However, after the publication of the Cardiac Arrhythmia Suppression Trial (CAST) in 1991 [32], as mexiletine is a class I antiarrhythmic agent, it was suspected that it could induce arrhythmia or accentuate a pre-existing arrhythmia. For this reason, several contraindications were included in the mexiletine summary of product characteristics [13]: (1) ventricular tachyarrhythmia; (2) complete heart block (i.e. third-degree AVB) or any heart block susceptible to evolve to complete heart block (first-degree AVB with markedly prolonged PR interval [≥ 240 ms] and/or wide QRS complex [≥ 120 ms], second-degree AVB, bundle branch block, bifascicular and trifascicular block); (3) myocardial infarction (acute or past) or abnormal Q-waves; (4) symptomatic coronary artery disease; (5) heart failure with mid-range (40–49%) and reduced (< 40%) ejection fraction; (6) atrial tachyarrhythmia, fibrillation or flutter; (7) sinus node dysfunction (including sinus rate < 50 beats/min); and (8) co-administration with medicinal products inducing torsades de pointes or those with a narrow therapeutic index.

4.1. Mexiletine in myotonic dystrophy

In France, patients with DM currently have access to mexiletine under a compassionate use protocol [14]. Although preclinical animal studies did not reveal any special hazards, these studies were not performed in accordance with current standards. Indeed, it is always delicate to extrapolate animal studies to humans, and thus the cardiac risk cannot be ruled out entirely [13]. However, in humans, mexiletine has been used for decades to treat arrhythmia and myotonia. A recent systematic review of 221 studies with 8970 patients treated with mexiletine for different conditions (including DM) has shown that its use is both effective and safe [30].

Various studies support the innocuity of mexiletine on cardiac function in patients with myotonic disorders [32–42]. These studies included selected populations who were generally assumed to be at low risk of cardiac complications. Overall, 236 patients with non-dystrophic myotonic have been included in three randomized controlled trials [38–40] and two retrospective studies [36,37] with mexiletine doses of 200–600 mg/day for up to 20 years. None of these studies raised any safety concerns. Furthermore, results from studies in patients with DM support the safety of mexiletine use. Several trials supporting the safety and tolerability of mexiletine use in patients with DM are summarized in Table 1 [35,41–44].

There are two ongoing clinical trials that should further provide information on the safety profile of mexiletine. The MIND study (ClinicalTrials.gov identifier: NCT04700046) is a phase 3, randomized, double-blind, placebo-controlled, multicentre study that aims to investigate the long-term efficacy and safety of mexiletine in patients with DM1 or DM2. Another phase 3, paediatric, open-label, multicentre, single-arm, interventional study (ClinicalTrials.gov identifier: NCT04624750) will provide the first data on patients with DM aged < 18 years.

5. Methods

In France, healthcare of neuromuscular disorders is managed by competence and reference centres that are organized into three regions (northeast Île-de-France, west of France and southeast of France) and led by the Rare Diseases network, FILNEMUS (https://www.filnemus.fr/). In the expert group, each region was represented by a neurologist specialized in DM and/or a referring cardiologist for cardiac assessment in neuromuscular diseases. Four successive expert meetings were held between December 2021 and October 2022. The experts aimed to define the screening and surveillance tools required to detect arrhythmia or any cardiac safety signals in patients with DM starting mexiletine or under mexiletine treatment.

In the first meeting, the scientific committee included three neurologists specialized in myotonic disorders (G. B., E. S.-C., S. V.), two referring cardiologists for cardiac assessment in neuromuscular diseases (K. W., F. L.) and one pharmacologist researcher specialized in voltage-gated ion channel impairment and voltage-gated sodium channel blockers (J.-F. D.); they defined the needs and issues in cardiac assessment and decision-making regarding the use of mexiletine in adult patients with DM.

A review of the literature using key words was conducted using the PubMed database to retrieve English and French language articles published up to 01 October 2021 (randomized controlled trials, meta-analyses, systematic reviews and observational studies). The following search terms were used: "mexiletine"; "myotonic dystrophy" AND "mexiletine"; "non-dystrophic myotonia" AND "mexiletine"; "mexiletine" AND "tolerance"; "mexiletine" AND "safety cardiac"; "cardiac safety" AND "mexiletine"; "myotonia" AND "mexiletine" AND "safety"; "myotonia" AND "mexiletine" AND "safety cardiac"; "cardiovascular" AND "mexiletine" AND "myotonia"; "cardiovascular" AND "mexiletine" AND "myotonic dystrophy"; "cardiovascular" AND "mexiletine" AND "non-dystrophic myotonia"; and "mexiletine" AND "adverse events".

Five publications corresponding to the selection criteria (i.e. clinical studies with safety data recorded on mexiletine in patients with and without DM) were analysed and discussed by the members of the scientific committee [35,41–44]. The mexiletine compassionate use protocol closely related to the summary of product characteristics was also reviewed. Working axes were established, and it was decided that an algorithm would be developed to provide practical guidelines for mexiletine initiation and decision making during follow-up. The second and third meetings were dedicated to the development of the algorithm for patients with DM. Considering the importance of cardiac clinical issues, three additional experts in cardiology and neuromuscular disease joined the expert group (J.-C. D., J. D., J.-M. S.) to help to develop the algorithm. A first algorithm was reviewed and amended during the third workshop. During the fourth (final) workshop, the algorithm was presented to neurologists and cardiologists from 20 FILNEMUS neuromuscular reference centres. Overall, 33 practitioners (neurologists and cardiologists) from the French neuromuscular centres adjudicated the algorithm, which resulted in several modifications to produce the final algorithm.

6. Expert opinion

General recommendations on the cardiac monitoring of patients with DM have been issued by international societies [5,6]. However, no specific recommendations exist for the decision of whether to treat myotonic symptoms with mexiletine or for the cardiac follow-up of patients with DM who are taking mexiletine. The experts agreed that the cardiac monitoring schedule should be divided into two phases: (1) the initiation of treatment, including titration until the maximum effective dosage has been reached; and (2) a long-term monitoring phase.

6.1. Initiation of mexiletine in patients with DM (Central Illustration)

The decision to initiate treatment with mexiletine should always be preceded by a complete work up by a cardiologist to screen for any cardiac contraindications to treatment. Any personal history of myocardial infarction, angina/non-revascularized coronary artery disease, high-grade AVB without permanent pacing, atrial fibrillation, atrial flutter or use of drugs that may cause torsades de pointes (class Ia, Ic and III antiarrhythmics) are absolute contraindications to treatment initiation [13]. It should be noted that experts believe that revascularized coronary disease without sequelae of infarction is not an absolute contraindication, and that patients with implantable cardioverter defibrillator or pacemaker devices and high-grade AVB must be screened for concomitant ventricular rhythm disorders.

At a minimum, cardiac evaluation should include an electrocardiogram, echocardiography and 24-hour Holter electrocardiogram monitoring. If deemed necessary, the cardiologist can also perform an electrophysiological study as well as screening for coronary disease. Findings of at least one electrocardiogram abnormality, such as sinus bradycardia (heart rate < 50 beats/min), PR interval ≥ 240 ms or QRS duration ≥ 120 ms, bifascicular/trifascicular block, high-degree AVB, ventricular tachycardia, atrial fibrillation, atrial flutter, Q waves on the electrocardiogram secondary to a personal history of myocardial infarction or repolarization abnormalities are absolute contraindications to mexiletine initiation. It must be noted that, although sustained ventricular tachycardia is an absolute contraindication, in case of non-sustained ventricular tachycardia, the mode of diagnosis (pacemaker or Holter), the presence of symptoms and triggering favourable factors (hydroelectrolytic disturbances to be normalized when possible) can influence the decision. Abnormalities in the echocardiography (left ventricular ejection fraction < 50% or regional wall motion abnormality) will also prevent treatment initiation. In case of a PR interval > 200 ms or QRS > 100 ms, initiation of treatment should only begin after close assessment of the risk/benefit balance.

After treatment initiation, an electrocardiogram is recommended at 1 week after each dose modification (average mexiletine half-life of 10 hours), as mentioned in the current compassionate usage guideline, until the maximal effective dose is reached. This follow-up electrocardiogram does not need to be performed in a hospital, and can be performed by any cardiologist in charge of the patient. If any symptoms arise, advice from a cardiologist must be sought. Onset of any rhythm disorder, conduction disorder or QRS widening > 25% must lead to either a decrease in dosage or discontinuation.

6.2. Follow-up of patients with DM (Central Illustration)

As per the algorithm, if no new cardiac symptoms arise, such as chest pain, unusual palpitations or syncope, treatment can be continued, and it is recommended to perform an electrocardiogram at least once per year – or more often if deemed necessary by the physician. Patients and family members should be educated about the importance of recognizing new symptoms. Optional annual tests, depending on the context and at the discretion of the physician, can include echocardiography, Holter electrocardiogram, electrophysiological exploration or coronary disease screening as recommended by the ESC guidelines [6].

Advice from a cardiologist must be sought if any cardiac symptoms arise. Onset of any rhythm disorder, conduction disorder or QRS widening > 25% must lead to either a decrease in dosage or discontinuation. When needed, advice from a referent cardiologist should be sought. When no cardiologists are involved in a competence or reference centre for neuromuscular disorders, advice can be sought from the national multidisciplinary team meeting (*Réunion de concertation pluridisciplinaire*), which is under the auspices of the FILNEMUS network, one of the 23 national networks that coordinate care of rare diseases in France.

7. Dissemination

An original algorithm was developed to facilitate the decision making when initiating or continuing mexiletine treatment in adult

patients with DM. During the last workshop, the algorithm was presented to a large assembly of French neurologists comprising 33 physicians from 20 expert centres in neuromuscular disorders. From this meeting, it was apparent that there is great heterogeneity in patient management regarding mexiletine treatment among the different centres, and that this expert opinion document would be highly welcomed. Some comments were raised, and all of them were integrated into the final algorithm (Central Illustration). The suggestion was made to leave some flexibility for the realization of the control electrocardiogram after initiation, as mexiletine titration can be adjusted according to the patient. In addition, it was proposed that the electrocardiogram could be performed in the centre or in private practice to give the patient more flexibility.

8. Discussion

Patients with DM have a high risk of cardiac involvement; however, the frequent and known cardiac evolution of the disease must not systematically contraindicate treatment with mexiletine. Myotonia – which can arise in all five forms of DM1 and can affect patients severely [3,17,42] – is often one of the first symptoms, whereas cardiac impairment often occurs later in the DM1 natural history.

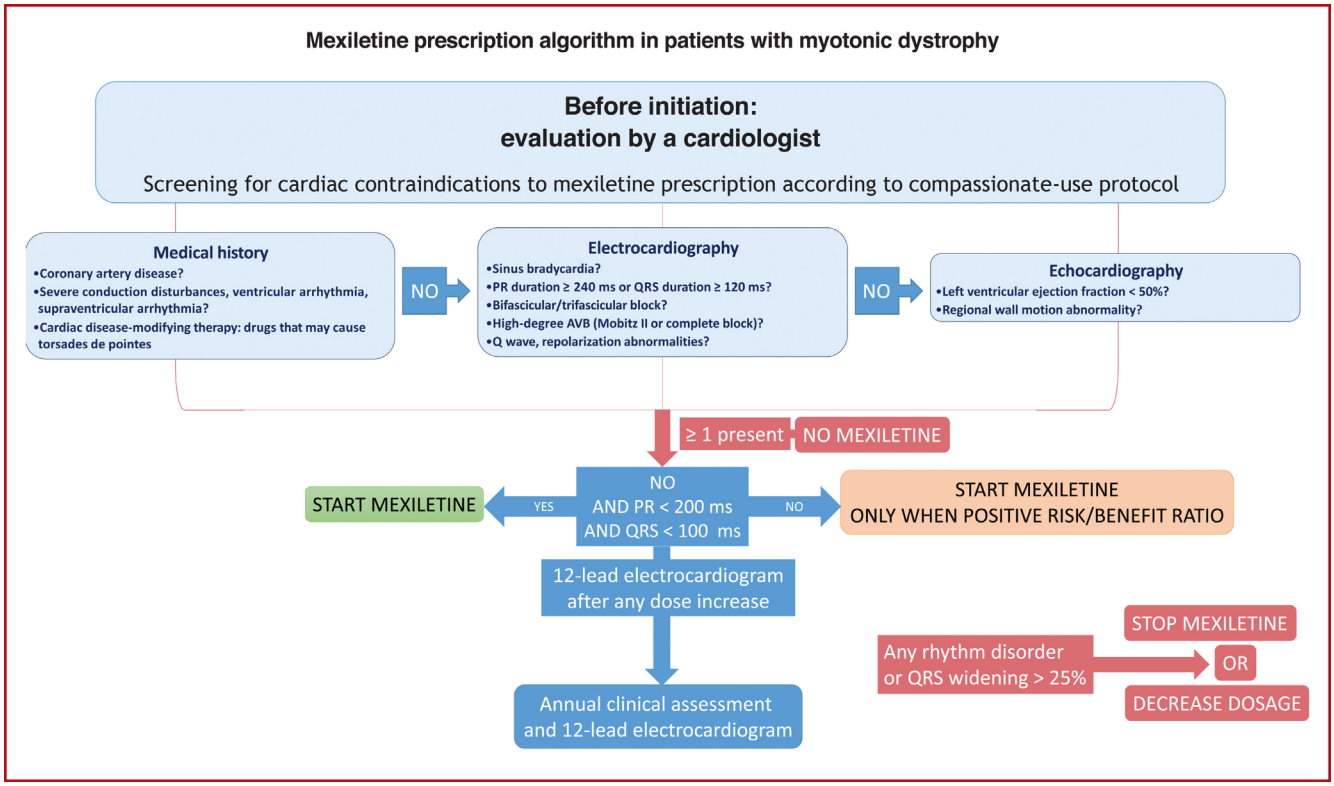
Historical studies [32,33] have highlighted an increased risk of sudden deaths with some class I antiarrhythmic agents in patients with ischaemic heart disease or heart failure. The results of these studies, which have been extrapolated to all class I agents (including mexiletine), and the pathophysiology of arrhythmic manifestations of DM involving a sodium current dysfunction have raised some concerns regarding the use of mexiletine in patients with DM. However, published clinical studies on the use of mexiletine in DM have been reassuring, without evidence of a significant risk of cardiovascular events in selected patients with DM with normal cardiac assessments or only mild cardiac abnormalities. The most recent data on the real-life use of mexiletine [35,43,44] in patients with DM also showed no major cardiac effects, e.g. arrhythmias, major conductive defects or sudden death. Although the samples of patients in these studies are small, additional data should be provided in the future through the national French DM Registry (DM-Scope), which includes information on mexiletine usage and cardiac outcomes.

Based on the scientific literature on this topic, the official information available on mexiletine [13,14] and the expertise of the authors, a decision support algorithm has been developed. Three patient subgroups have been identified: (1) patients with a low cardiac risk who can benefit fully from mexiletine; (2) patients with a mild cardiac risk who could benefit from mexiletine following consultation between a neurologist and a cardiologist to assess the benefit/risk ratio; and (3) patients with a high cardiac risk, for whom treatment is contraindicated or strongly discouraged.

This algorithm underlines the importance of the dialogue between cardiologists and neurologists in decision making for mexiletine treatment initiation and cardiac monitoring under treatment. Development of such recommendations at the European level could help to improve the management of patients with DM.

9. Conclusion

An algorithm has been developed to guide the use of mexiletine to treat myotonia in patients with DM to reduce the risk of cardiovascular adverse events (Central Illustration).



Central Illustration. Use of mexiletine for adults with myotonic dystrophy. AVB: atrioventricular block.

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Disclosure of interest

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