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Recommendations of an expert group for the cardiac assessment of non-dystrophic myotonia adult patients treated with mexiletine

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ABSTRACT

Mexiletine (NaMuscla™) is indicated for the symptomatic treatment of myotonia in adults with non-dystrophic myotonia. A cardiac assessment is required as mexiletine may have a pro-arrhythmic effect. Long-term safety data supporting the use of mexiletine in patients with non-dystrophic myotonia combined with the extensive clinical experience of an expert group resulted in creation of an algorithm for cardiac monitoring of patients treated with mexiletine. To define the treatment algorithm, several expert workshops including three neurologists, five cardiologists from different French neuromuscular reference centers and one pharmacologist from Italy were set up. These workshops aimed to define the screening and surveillance tools required to ensure the safe use of mexiletine in patients. The recommendations are based on the summary of product characteristics (SmPC), a review of the literature on the safety of mexiletine-treated patients with non-dystrophic myotonia, and the expertise of the authors. The expert group concluded that the cardiac safety profile of mexiletine in these patients appears to be similar to that in the general population. Therefore, patients with non-dystrophic myotonia treated with mexiletine should be monitored as per any patient with cardiac problems who are prescribed a class 1b anti-arrhythmic.

1. Introduction

Non-dystrophic myotonias (NDMs) are rare hereditary neuromuscular disorders caused by mutations in gene coding for skeletal muscle voltage-gated channels leading to delayed muscle relaxation after voluntary contraction [1]. The prevalence of NDM is estimated at 1.92 per 100,000 population [2] and its most common clinical feature consists of myotonia causing functional limiting stiffness, pain, fatigue, and weakness [3]. In contrast to the type 1 and type 2 dystrophic myotonias (DMs), NDM does not present with multisystem complications, including cardiac manifestation [4].

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No disease-modifying therapy is currently available for myotonic patients in a routine care setting, but several drug candidates that aim to relieve myotonic symptoms are under investigation [5]. Mexiletine, a cardiac antiarrhythmic agent which belongs to the voltage-gated sodium channel blockers class 1 b of the Vaughan-Williams classification [6], has been prescribed in myotonic disorders for over 30 years [7], and then has been repurposed to attenuate myotonia in DM and NDM patients. It is the only antimyotonic drug approved for NDM adults since 2018 by the European Medicines Agency (EMA) and more recently by the United Kingdom [8].

However, as mexiletine belongs to class 1 antiarrhythmics, concerns regarding its usage in DM and NDM patients about possible pro-arrhythmogenic effects and long-term cardiological safety persist.

This work provides expert opinion on the use of mexiletine in patients with NDM, aiming to assist physicians (both neurologists and cardiologists), via an algorithm, in decision-making before initiating mexiletine and follow-up care after initiation. A similar work was conducted in parallel for DM patients and addressed in a dedicated publication [9].

2. Non-dystrophic myotonias

The NDMs belong to skeletal muscle channelopathies and include myotonia congenita (or Becker and Thomsen myotonia congenita), paramyotonia congenita (or Von Eulenburg paramyotonia), sodium channel myotonias, and hyper/normokalemic periodic paralysis with myotonic symptoms. Myotonia congenita, the most common skeletal muscle channelopathy, can be autosomal dominant or autosomal recessive, and is caused by a mutation in the CLCN1 gene encoding for the main skeletal muscle chloride channel CIC-1. Paramyotonia congenita and sodium channel myotonias are autosomal dominant and are caused by mutations in the SCN4A gene, which encodes the skeletal muscle sodium channel Nav1.4 [10].

NDMs are characterized by delayed muscle relaxation leading to muscle stiffness, which impairs mobility and can result in falls. Patients also frequently report pain, fatigue, and weakness [3,4]. Pediatric forms of NDMs include the Severe Neonatal Episodic Laryngospasms (SNEL) phenotype, which can be life threatening [11]. Clinical symptoms can vary from mild to severe, with some patients only impacted during certain periods of their life (e.g. during pregnancy) or when exposed to exacerbating factors (e.g. cold, exercise, or fasting), while others have severe chronic stiffness that significantly impairs daily function and quality of life if untreated [12]. Fluctuation of symptoms along with the difference between how patients present in a clinical consultation in a warm indoor setting versus the challenges they may face when dealing on a daily basis mean that a personalized approach to treatment must be considered [12].

Unlike patients with DM, those with NDMs do not manifest with progressive weakness, muscle wasting, and multisystemic involvement and more particularly of the cardiac system [10].

The diagnosis of NDM is based on symptoms, the presence of electrical myotonia on electromyography (EMG), and genetic analysis [12]. Creatine kinase levels can be normal to mildly elevated. EMG functional tests with the repeated short exercise test and long exercise test (standardized exercise in combination with determination of compound muscle action potential amplitude or area) can help to further characterize the NDM phenotype [13,14]. Muscle magnetic resonance imaging (MRI) may reveal non-specific abnormalities potentially serving as a marker for disease progression in clinical trials [15].

Therapeutic options in NDM should target the underlying channel defect (CLCN1 or SCN4A) [16] that is translated to a gain of function when it is due to sodium channel mutations or to a loss of function in case of chloride channel mutations. Pharmacological treatment could therefore theoretically aim to increase chloride conductance and/or reduce sodium channel openings. Since there have been no successful chloride channel openers, most pharmacological agents used to treat myotonia are sodium channel blockers [17], which are effective by decreasing sarcolemma excitability, regardless of the specific channel defect. The first-line treatment of NDM is mexiletine [18], which has obtained an orphan drug designation in Europe and the United States. Other off-label therapeutic options include anti-epileptics, anesthetics, and other anti-arrhythmic drugs [12].

3. Mexiletine

Mexiletine has a close structural resemblance to lidocaine and possesses a wide range of therapeutic properties including local anesthetic, anticonvulsant, antiarrhythmic, and anti-myotonic effects. Initially developed as an anticonvulsant, mexiletine is classified as a class 1b antiarrhythmic agent by the Vaughan-Williams system. For over 45 years, cardiologists have used it to treat effectively cardiac arrhythmias like ventricular tachycardia (VT), ventricular fibrillation, and also long QT syndrome type 3 due to SCN5A gene mutations [6,19-21].

Class 1 agents primarily target the voltage-gated cardiac sodium channel NaV1.5, while class 1b drugs inhibit the late component of the sodium current (I_{Na}). Thus, these drugs shorten the duration of action potential and prolong the effective refractory period, reducing the risk of arrhythmia. However, despite the widespread clinical use of class 1 agents, their effectiveness can vary significantly and, in some cases, may even induce a proarrhythmic response [6]. For instance, the Cardiac Arrhythmia Suppression Trial (CAST) revealed that the use of two class 1c drugs to treat arrhythmia – encainide or flecainide – resulted in a higher incidence of adverse events (including deaths due to arrhythmia) compared to placebo [22]. This increased mortality risk was further supported by the results of a meta-analysis of quinidine, a class 1a agent [23]. Consequently, the observed rise in sudden deaths was extrapolated to all class 1 agents, including mexiletine despite it not being part of the drugs tested in those trials.

However, concerns were raised regarding mexiletine potential induction of arrhythmia or exacerbation of pre-existing arrhythmias. Consequently, when mexiletine received the European Marketing Authorization for the treatment of NMD adult patients in 2018, marketed as NaMuscla, several contraindications were implemented in the SmPC, including ventricular tachyarrhythmia and complete heart block (i.e. third-degree atrioventricular block [AVB]) or any heart block with the potential to progress 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, and bifascicular and trifascicular block). Other contraindications include acute or past myocardial infarction; presence of abnormal Q-waves; symptomatic coronary artery disease; heart failure with mid-range (40–49 %) or reduced (<40 %) ejection fraction; atrial tachyarrhythmia, fibrillation, or flutter; sinus node dysfunction (including sinus rate <50 bpm); and co-administration with medications that induce torsades de pointes or have a narrow therapeutic index [24].

4. Mexiletine in NDM

Mexiletine acts by non-selectively blocking sodium channels to restore muscle fiber membrane activity to a level close to normal. It also targets sodium channel Nav1.4 involved in the

Table 1
Studies of mexiletine use in patients with NDM.

Study	Statland et al. [3]	Stunnenberg et al. [27]	Vicart et al. [29]	Suetterlin et al. [28]	Modoni et al. [30]
Design	Double-blind crossover RCT	Aggregated N-of-1 RCTs	Double-blind crossover RCT	Retrospective review	Retrospective review
n	59	30	26 enrolled; 25 treated	63	112
Genetic testing	34 CLCN1 21 SCN4A 4 unknown	19 CLCN1, 11 SCN4A	13 CLCN1, 12 SCN4A	40 CLCN1, 21 SCN4A 2 mixt [a]	48 CLCN1 11 SCN4A
Dosage	600 mg/day	600 mg/day	600 mg/day	≤600 mg/day	200–600 mg/day
Comparator	Placebo	Placebo	Placebo	None	None
Duration	4 weeks mexiletine; 4 weeks placebo	Multiples of 4 weeks mexiletine; 4 weeks placebo	18 days mexiletine; 18 days placebo	Mean (range): 4.8 (0.5–17.8) years	1 month to 20 years
Countries	USA, Canada, UK, Italy	The Netherlands	France	UK	Italy
Cardiovascular events	Two participants experienced transient cardiac effects that did not require them to stop the study (1 in each group)	No clinically relevant electrocardiographic rhythm abnormalities or cardiac conduction interval changes	No serious cardiovascular AEs. Palpitations (during a stressful situation) led to mexiletine discontinuation in one patient with myotonia congenita but resolved spontaneously within a few hours. There were no significant variations in 12-lead ECG or portable ECG device parameters (heart rate, PR, QRS, QTc) from baseline to the end of treatment	Heart rate, PR interval, QRS duration, and QTc were not significantly different at maximum mexiletine dose vs no mexiletine	No arrhythmia reported
Other safety events	The most common AE was gastrointestinal (9 mexiletine, 1 placebo). One serious AE (narcotic withdrawal) was determined not to be related to the study	The most common AE was gastrointestinal discomfort (21 mexiletine, 1 placebo). One serious AE (allergic skin reaction) on mexiletine	No serious AEs. The most common AE was gastrointestinal disorders (7 mexiletine, 2 placebo)	No serious AEs. The most common AE was dyspepsia (23 patients)	The most common AE was dyspepsia (17 mild, 4 moderate, 4 severe = discontinued)

AE, adverse event; CLCN1, skeletal muscle chloride channel gene; ECG, electrocardiogram; n, number of patients enrolled; NDM, non-dystrophic myotonia; RCT, randomized controlled trial; SCN4A, skeletal muscle sodium channel gene; UK, United Kingdom; USA, United States of America.
[a] combination of CLCN1 and SCN4A mutations.

hyperexcitability of the muscle fiber membrane. Its inhibitory potency is particularly enhanced in situations of bursting action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block) that are commonly observed in affected tissue, rather than during normal physiological excitability (resting or tonic block) [25,26].

Preclinical animal studies have not revealed any specific hazards due to mexiletine intake [24] but extrapolating animal data to humans remains challenging and thus cardiac risk cannot be entirely ruled out [24].

Various studies support the innocuity of mexiletine on cardiac function in NDM population generally assumed to be at low risk of cardiac complications [3,25,27-30]. Overall, 236 patients with NDM have been enrolled in three randomized controlled trials (RCTs) [3,27,29] and two retrospective studies [28,30]. The mexiletine doses ranged from 200 mg/day to 600 mg/day and the treatment duration extended up to 20 years. None of these studies raised any safety concerns; specifically, no cardiac arrhythmia cases were captured (Table 1).

One case of bradycardia was reported in the first RCT, which was published in 2012 (i.e. before the EMA approval). It occurred at the end of Week 4 and resolved during follow-up without stopping treatment [3]. Those data are supported by two other RCTs [27,29], which have demonstrated the efficacy and safety of mexiletine for NDM without any serious cardiac adverse events associated with mexiletine use in NDM patients reported. In the N-of-1 trials, no clinically relevant variations were observed in electrocardiogram (ECG) readings at the end of the treatment period [27].

In a long-term retrospective patient cohort data study of mexiletine for NDM (n = 59; treatment duration 1 month to 20 years), no patients developed cardiac arrhythmias [28]. In another retrospective study (n = 63), ECG recordings found no significant changes in P wave to beginning of QRS complex interval, heart rate, QRS duration, or corrected QT interval when taking mexiletine compared to baseline. Sixteen patients were referred to a cardiologist due to cardiac concerns prior to or during mexiletine administration but all were medically cleared to start or continue treatment [30]. In a third study, 37 patients with NDM used an antimyotonic medication, mostly mexiletine or ranolazine, with no reported cardiac adverse events [31].

Moreover, a recent systematic review that included 221 studies with 8970 patients treated with mexiletine for different conditions has shown that mexiletine use is both effective and safe at doses ranging from 50 mg/day to 2400 mg/day [20].

5. Methods

In France, the healthcare of patients with neuromuscular disorders is managed by reference and competence centers in three regions (North-East-Ile-De-France, West France, and Southeast France), all belonging to the Rare Diseases network dedicated to neuromuscular disorders, Filnemus (https://www.filnemus.fr/). In the expert group, each region was represented by a neurologist specializing in myotonic disorders including the national reference center for muscle channelopathies and/or a referring cardiologist for cardiac assessment in neuromuscular diseases. Four expert

meetings were held between December 2021 and October 2022. The experts aimed to define the screening and monitoring tools required to detect arrhythmia or any cardiac safety signals in patients with NDM starting or undergoing mexiletine treatment.

During the first meeting, the scientific committee – including three neurologists specialized in myotonic disorders (GB, ES-C, SV), two referring cardiologists for cardiac assessment in neuromuscular diseases (KW, FL), one pharmacologist researcher specialized in voltage-gated ion channel impairment and voltage-gated sodium channel blockers (J-FD) – defined the needs and issues in cardiac monitoring and decision making regarding mexiletine therapy in adults with NDM.

A review of the literature using key words was conducted using the PubMed database to retrieve English and French language articles published up to 1 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”.

A total of 2310 publications were found, which was reduced to 1980 after removal of duplicates and to 10 after removal of irrelevant titles, abstracts, and case reports. Five publications [3,27-30] corresponded to the selection criteria i.e. clinical studies with safety data recorded on mexiletine in patients with NDM (Fig. 1).

Two experts (J-FD and KW), evaluated each article separately, extracted the safety data, and presented them to the members of the scientific committee. The mexiletine summary of product characteristics (SmPC) was also reviewed. The committee decided to develop an algorithm that would provide practical guidelines for initiating mexiletine treatment and making decisions during follow up.

The second and third meetings were dedicated to refining the algorithm. Considering the importance of cardiac clinical issues, three additional referring cardiologists for myotonic disorders (JCD, JD, JMS) joined the expert group. The five cardiologists represent at least 30% of the French neuromuscular centers who have a referring cardiologist. Discussions among experts continued between the meetings and led to the proposal of an algorithm during the third meeting that was reviewed and amended by all the experts. In the final meeting, the algorithm was presented to neurologists and cardiologists from 20 neuromuscular reference and competence centers of Filnemus. Overall, 33 practitioners (neurologists and cardiologists) from the neuromuscular centers were involved with the algorithm and all suggestions were included in the final version presented here.

6. Expert opinion

Although cardiac abnormalities have been reported in NMD patients with SCN4A or CLCN1 mutations [32], these were most often isolated observations in elderly patients with other comorbidities that could explain the cardiac abnormalities found [33], or benign cardiac abnormalities such as isolated premature atrial beats [34]. While caution is advised, the NMD population does not appear to be at a higher risk of arrhythmia or conduction disorders than the general population.

The available literature on mexiletine [3,27-30], including RCTs and real-life data in large cohorts, provides reassurance regarding its cardiac safety in this population, regardless of the gene involved (Table 1). The cardiac assessment should therefore focus on identifying "general" contraindications, as would be done for a patient without any myotonic syndrome. Monitoring should consider the patient’s age, with more frequent monitoring for older patients. The experts agreed that the cardiac monitoring schedule should be divided into two phases: the initiation of treatment, which includes titration until reaching the therapeutic dosage, and a long-term monitoring phase.

To facilitate decision-making when initiating or following up adult patients with NDM on mexiletine treatment, an algorithm has been designed (Fig. 2). This algorithm provides a step-by-step approach to guide healthcare professionals in the management of mexiletine therapy in this patient population.

6.1. Initiation of mexiletine treatment in patients with NDM

The decision to initiate treatment with mexiletine should always be preceded by a comprehensive evaluation by a cardiologist to screen for any cardiac defects.

Any history of myocardial infarction, angina/non-revascularized coronary artery disease, high-grade AVB without permanent pacing and use of drugs that may cause torsades de pointes (classes 1a, 1c, and 3 antiarrhythmics as described in the SmPC [24]) are contraindications to mexiletine treatment initiation. It should be noted that revascularized coronary disease without sequelae of infarction is not considered as an absolute contraindication. In addition, patients with implantable cardioverter defibrillators or pacemakers and high-grade AVB must be screened for concomitant ventricular rhythm disorders.

Cardiac evaluation should include a systematic ECG and echocardiography. Given the absence of an increased risk of cardiac complications, a fortiori with prognostic consequences, in NDM patients compared to the general population, the added value of systematically performing a Holter-ECG prior to treatment initiation to detect cardiac abnormalities is very low, particularly if the ECG and echocardiography are normal. However, as in the general population without genetic disease, Holter-ECG and other investigations could be performed at the cardiologist’s discretion.

Findings of at least one ECG abnormality – such as sinus bradycardia (heart rate $<$50 bpm), PR interval $\geq$240 ms or QRS duration $\geq$120 ms, bifascicular/trifascicular block, high-degree AVB, VT, atrial fibrillation, atrial flutter, necrosis Q waves, and repolarization abnormalities – are contraindications to mexiletine initiation. It is crucial to note that while sustained VT is an absolute contraindication, in case of non-sustained VT, the diagnosis mode (pacemaker or Holter), the presence of symptoms and favoring factors (hydroelectrolytic disturbances to be normalized when possible) can influence the treatment decision.

Echocardiography abnormalities (such as left ventricular ejection fraction $<$50% or regional wall motion abnormality) will also prevent treatment initiation.

After treatment initiation, it is recommended to perform an ECG once the most effective dose has been reached, usually 3 weeks after the first dose (Fig. 2). This control ECG does not need to be performed in a hospital and can be done in private practice. If any symptoms arise during the titration period and/or ECG abnormalities appear on the ECG, advice from a cardiologist must be sought.

6.2. Follow-up of patients with NDM

If no ECG abnormalities are noted and no new symptoms arise (e.g. chest pain, unusual palpitations, or syncope), mexiletine treatment can be continued, and it is recommended that a

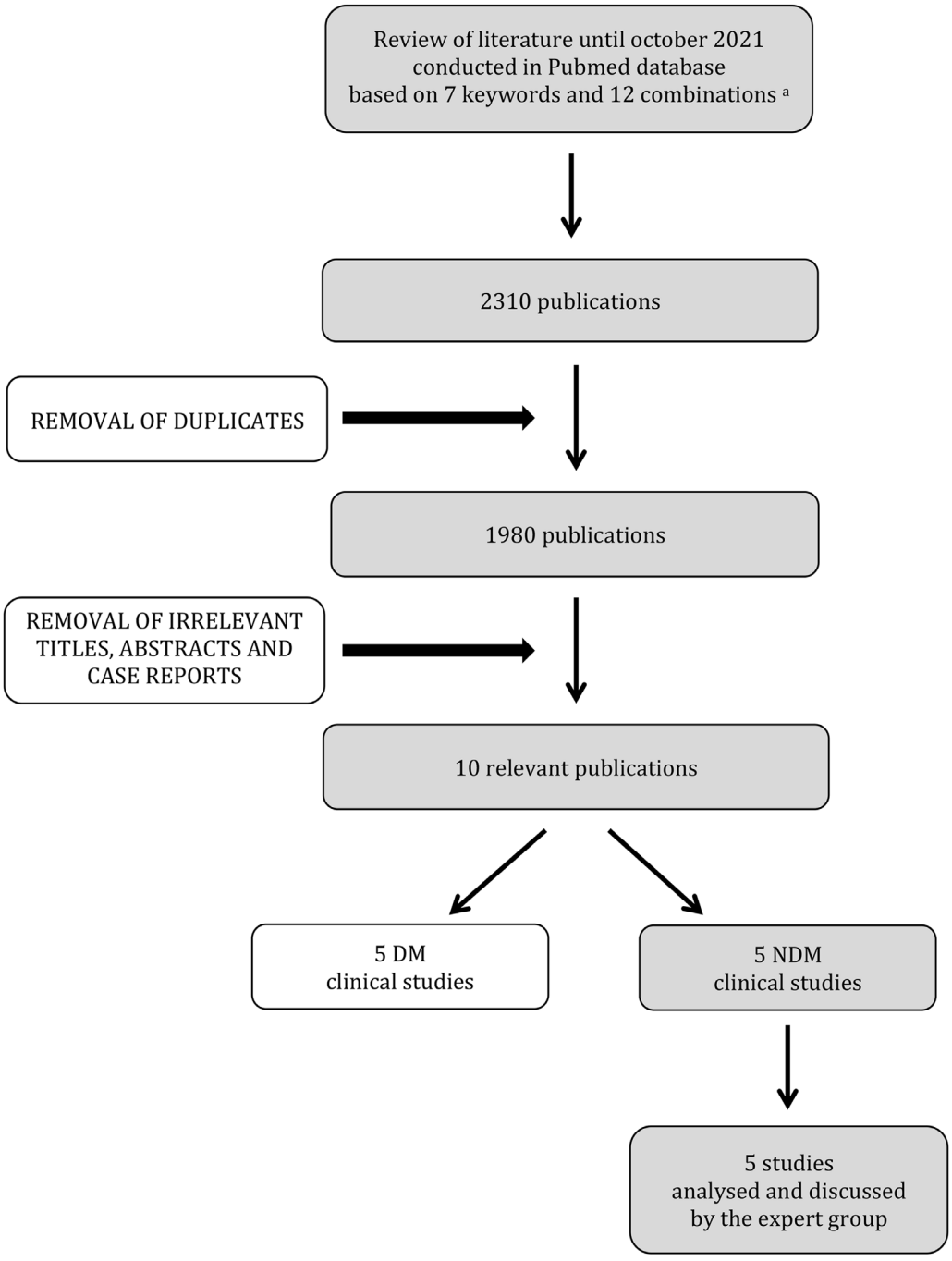

Fig. 1. Literature review strategy and filtering steps flowchart diagram.
[a] "mexiletine"; "myotonic dystrophy" AND "mexiletine"; "non-dystrophic myotonia" AND "mexiletine"; "mexiletine" AND "tolerance"; "mexiletine" AND "safety cardiac"; "cardiac safety" AND "mexiletine"; "myotonia" AND "mexiletine" 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". DM, dystrophic myotonia; NDM, non-dystrophic myotonia

neurologist or cardiologist perform an ECG every 2 years, or more frequently if deemed necessary. It is recommended to perform an ECG and echocardiography every year in patients with known pre-existing cardiac abnormalities, which do not contraindicate mexiletine initiation. Patients and family members should be educated about the importance of recognizing new symptoms and promptly reporting them to the healthcare provider.

A systematic cardiology consultation every 5 years is recommended for cardiovascular risk assessment and screening for coronary artery disease following ESC guidelines [21].

7. Dissemination

During the last workshop, the algorithm was presented to a large assembly of French neurologists comprising 33 physicians from 20 expert centers in neuromuscular disorders. It arose from this meeting that there is a great heterogeneity in patient management regarding mexiletine treatment among the different centers and this expert opinion document would be highly welcomed. Some comments were raised and all of them were integrated into the algorithm. It was suggested to leave some

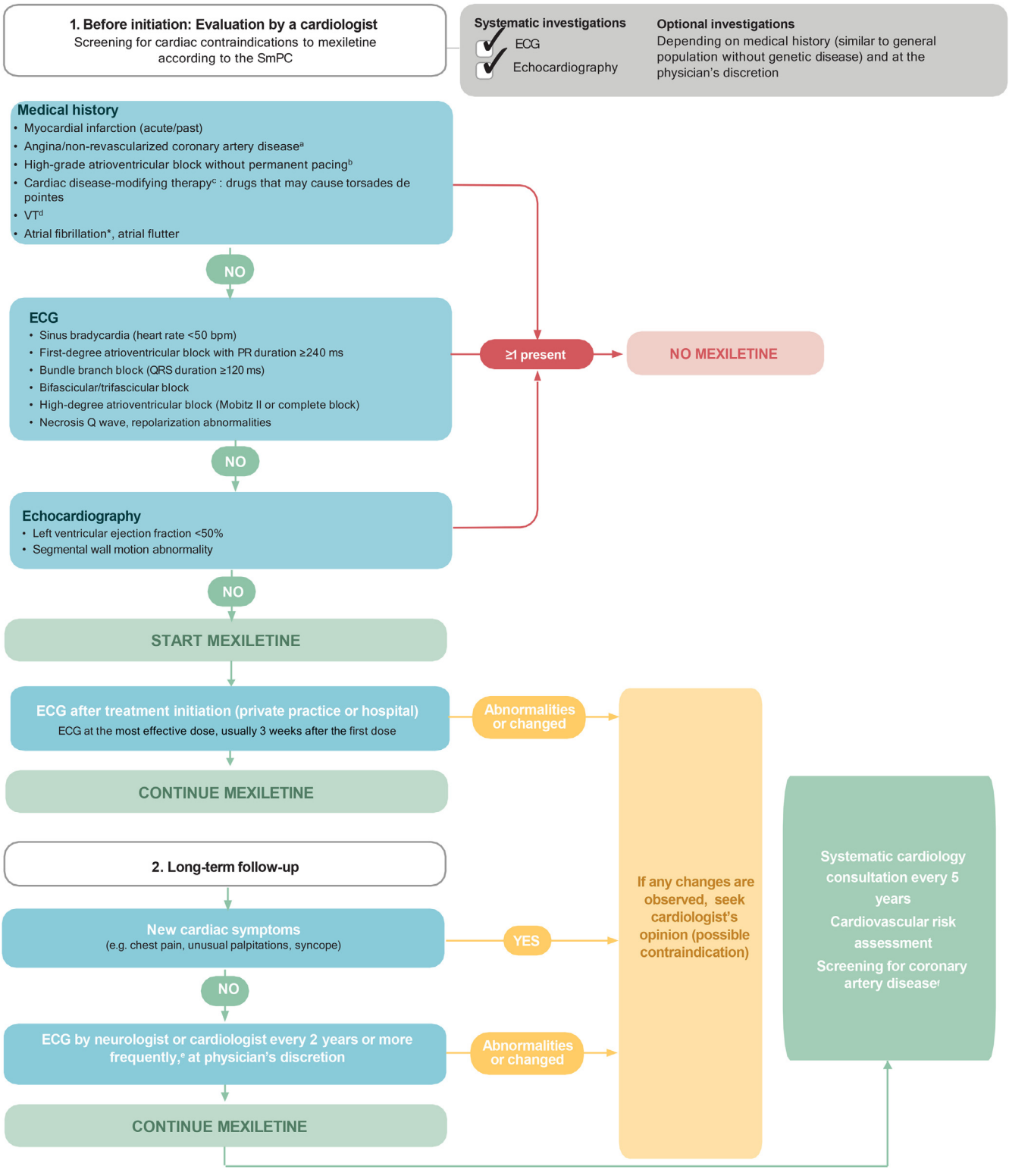

Fig. 2. Use of mexiletine in adult patients with NDM.
[a] Revascularized coronary disease without sequelae of infarction is not an absolute contraindication, [b] For patients with high-grade atrioventricular block with a device, concomitant presence of ventricular rhythm disorders must be checked, [c] Mexiletine SmPC: https://www.ema.europa.eu/en/documents/product-information/namuscla-epar-product-information_en.pdf, [d] Sustained VT is an absolute contraindication. For non-sustained VT, the decision can take into account the mode of diagnosis (pacemaker or Holter), the presence of symptoms and favouring factors (hydroelectrolytic disturbances to be normalized if possible), [e] Mexiletine SmPC recommends ECG + echocardiography every year in patients with known cardiac abnormality, or more frequently if deemed necessary, [f] According to 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: https://doi.org/10.1093/eurheartj/ehz425, *Original indication for mexiletine as an anti-arrhythmic but contraindicated in NaMuscla SmPC.
ECG, electrocardiogram; ESC, European Society of Cardiology; NDM, non-dystrophic myotonia; SmPC, summary of product characteristics; VT, ventricular tachycardia.

flexibility around the timing of the post-initiation ECG as mexiletine titration can be adjusted according to the patient. Following the discussion, it was added that the ECG could be performed in a hospital or in private practice to give the patient more flexibility.

8. Discussion/Conclusion

Unlike in myotonic dystrophies, patients with NDM do not have an elevated cardiac risk. Concerns about the use of mexiletine in patients with NDM were based on historical studies [22,23] that showed increased sudden deaths with certain class 1 anti-arrhythmic agents, which led to the extrapolation of these results to mexiletine.

Several published clinical studies on the use of mexiletine in patients with NDM, both chloride and sodium channelopathies, have shown reassuring cardiac data, including RCTs and retrospective studies with large patient cohorts [3,27-30]. These studies have confirmed the safety and efficacy of mexiletine for treating patients with NDM, regardless of the phenotype and the gene involved, with a significant improvement of stiffness [3,27,29] and, when it was assessed, of quality of life [29].

The proposed algorithm enables neurologists to prescribe mexiletine with confidence, and to propose a clear course of action. The literature, the official information available on mexiletine (SmPC), and the expertise from the authors have enabled us to develop a decision-support algorithm. This algorithm underlines the importance of collaboration between cardiologists and neurologists in decision-making for mexiletine treatment initiation and required cardiac monitoring in patients with NDM under treatment. The development of such recommendations at the European level could help to improve the management of patients with NDM.

Overall, the expert group's work and the algorithm they developed provide valuable support for the use of mexiletine in patients with NDM, addressing the concerns and heterogeneity in patient care while highlighting the favorable benefit-to-risk balance of mexiletine for myotonia.

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Declaration of competing interest

All authors declare consulting fees from Lupin Neuroscience.

CRediT authorship contribution statement

Savine Vicart: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Karim Wahbi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Josselin Duchateau:** Writing – review & editing, Validation, Methodology. **Jean-Marc Sellal:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Jean-François Desaphy:** Writing – review & editing, Validation, Data curation. **Jean-Claude Deharo:** Writing – review & editing, Validation, Methodology. **Guillaume Bassez:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Emmanuelle Salort-Campana:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Fabien Labombarda:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization.

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Abbreviations

AVB, atrioventricular block; CAST, Cardiac Arrhythmia Suppression Trial; CLCN-1, skeletal muscle chloride channel gene; DM, dystrophic myotonia; ECG, electrocardiogram; EMA, European Medicines Agency; ESC, European Society of Cardiology; EMG, electromyography; Nav1.4, voltage-gated skeletal muscle sodium channel; Nav1.5, voltage-gated cardiac sodium channel; NDM, non-dystrophic myotonia; RCT, randomized controlled trial; SCN4A, skeletal muscle sodium channel gene; SmPC, summary of product characteristics; VT, ventricular tachycardia.

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