Mexiletine in the Treatment of Non-dystrophic Myotonia: Interviews with Six Medical Experts

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Interview Summary

Evidence from randomised controlled clinical trials demonstrates that mexiletine effectively controls myotonic symptoms with a well-described safety profile. Despite this, there are still a limited number of patients on this treatment, and physicians from expert neuromuscular centres may not be fully aware of the potential benefits of mexiletine treatment, including improvements in patients' quality of life (QoL), the impact on activities of daily living, and the favourable safety profile, even in younger patients.

During this 'Meet the Experts' interview series, five neurologists experienced in the management of non-dystrophic myotonias (NDM), and one specialist cardiologist offered their expert insights on the clinical data and real-world evidence supporting the use of mexiletine in NDM.

Addressing patient concerns and encouraging treatment acceptance were highlighted as key steps to optimise outcomes from mexiletine therapy. The medical experts emphasised the importance of contextualising the favourable benefit-to-risk profile of mexiletine, particularly regarding cardiac safety concerns and drug monitoring requirements. The expert cardiologist further explained that, in their experience, the cardiac safety profile of mexiletine was no different in patients with NDM when compared to healthy controls used in clinical studies when used as directed.

When considering anti-myotonia treatment in patients with NDM, medical experts stressed that decision-making should be driven by the overall degree of myotonia. Healthcare professionals (HCP), therefore, need to look beyond basic clinical assessment to understand the true impact of myotonia on patients' everyday lives.

Overall, these interviews highlighted the critical role that HCPs can play in leveraging the clinical data and managing patient expectations to ensure maximum treatment success when recommending mexiletine to patients with NDM.

INTRODUCTION

NDM includes a group of rare hereditary neuromuscular disorders caused by mutations in the genes that encode sodium or chloride muscle channels.[1] Myotonia is the hallmark symptom of NDM and presents as muscle stiffness, often associated with pain, fatigue, and weakness, which can limit function.[2] Mexiletine is a Class IB antiarrhythmic medication, which has been shown to reduce muscle fibre excitability caused by common NDM mutations in preclinical models.[2] Mexiletine (NaMuscla® [Lupin Healthcare (UK) Ltd, Slough, UK]) is currently authorised by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of myotonia in adult patients with non-dystrophic myotonia disorders.[3]

This article captures the views of six medical experts who were posed questions on key topics relevant to the use of mexiletine in NDM as a part of a 'Meet the Experts' interview series conducted by Lupin Neurosciences (Zug, Switzerland). Five neurologists with a wealth of experience in the field were interviewed, as well as one expert cardiologist, who was questioned specifically on the cardiac safety profile and cardiac monitoring requirements with mexiletine.

THE RELEVANCE OF TREATMENT FOR MYOTONIA IN PATIENTS WITH NON-DYSTROPHIC MYOTONIAS AND PATIENT QUALITY OF LIFE

In the first part of this interview series, the NDM experts considered the relevance of the treatment of myotonia in patients with NDM, particularly the impact on QoL. QoL is an important issue for clinical consideration as evidence indicates that, although transient, symptoms such as myotonia exert a high impact on QoL in patients with NDM. In a study where QoL was assessed using the individualised QoL (INQoL) and Short Form 36 (SF-36) questionnaires, patients with skeletal muscle channelopathies showed similar scores and negative perceptions of QoL to those of patients with myotonic dystrophies.[4]

The five experts in neuromuscular disorders highlighted how symptoms of myotonia in patients with NDM could vary in frequency and severity, which may influence the clinical decision to treat. In particular, they noted the key factors that can trigger symptoms (e.g., cold weather or changes in outside temperature) and suggested how the timing and duration of treatment may be tailored accordingly. "I'll often suggest a short trial of treatment, if patients have significant symptoms; symptoms that are affecting their life, even if it's not every day, because often,

they won't realise some of the myotonia that's there in the background that they've been compensating for all their life," said Dipa Jayaseelan, University College London Institute of Neurology, UK. Jayaseelan also stated that "trying the treatment can really reveal to them how good they could be." Jordi Díaz Manera's, John Walton Muscular Dystrophy Research Center, Newcastle University, UK, clinical experience confirms that "patients [...] always have days that are better and days that are worse, although they always have like a certain degree of myotonia." Díaz Manera emphasised that "it's a question of discussing with them what can improve [...] and then in most of the cases, they will like to be treated."

The experts were unanimous on the importance of looking beyond the clinical assessment of myotonia in NDM and considering the broader impact on the daily lives of patients with NDM when making a decision about treatment. In particular, they highlighted the difference between how patients present in a clinical consultation in a warm indoor setting versus the challenges they may face when dealing with the symptoms of myotonia on a daily basis. Jayaseelan stated that "it's a hugely important part of the assessment, seeing how they are outside of the consultation and discussing what those symptoms are that they struggle with, and how treatment might help with those, and target it." Christiane Schneider-Gold, Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Germany, supported this point: "I think the impression you have from patient you see in your outpatient department or in your private practice may give you an impression of the severity of myotonia in general, but it may not reflect special situations in daily life. You have to listen carefully to the patient to get an overall impression of the disease and severity of disease in this particular patient." Valeria Ada Sansone, The NeMO Clinical Center, Neurorehabilitation Unit, University of Milan, Italy, further emphasised that it was important to "listen to the patients and see and hear what they tell you about how they're doing." Savine Vicart, Reference Center for Muscle Channelopathies, Service of Neuromyology, Pitié-Salpêtrière Hospital, Paris, France, cautioned that "clinical assessment of myotonia performed during a visit or consultation and the impact of the myotonic symptoms on the patient's daily life are not always correlated."

Alongside clinical and functional assessment tools, the experts highlighted the key questions that can help HCPs to better understand the burden of myotonia experienced by patients with NDM. This includes asking patients about their pain and fatigue, as well as probing the impact of myotonia symptoms on school or work life; sports; travel; and activities of daily life such as feeding and talking. As Jayaseelan elaborated: "For a patient, it's often very individual, the things that cause the myotonia to get worse and the things, the elements of their life, that the myotonia affects, and so we like to delve into those aspects to really understand how the myotonia is affecting them." Díaz Manera recommended asking patients to provide examples of how activities are influenced by the symptoms as it is "really useful to understand what's going on in the patient."

The experts stressed that understanding the true burden of myotonia symptoms and the associated impact on QoL was pivotal in determining which patients would benefit from anti-myotonia treatments such as mexiletine. "The decision to treat the patient with an anti-myotonia treatment is based on the individual type of myotonia and individual degree of the severity of myotonia and the individual challenges in the patient's life," noted Schneider-Gold. Although mexiletine is not a curative option for NDM, the experts agreed that it can have a significant positive effect in relieving disease burden, even in those patients who may not appreciate the true impact of the condition on their everyday lives. As Sansone explained: "I recommend mexiletine as the first line of choice to all patients with myotonia. I don't base myself on their channel pathology. If I see myotonia I suggest mexiletine, and I talk them into the action and why I'm giving it to them, and the safety profile and I try to make them think that they may feel better."

This point was reiterated by Vicart: "I consider that patients with NDM who will benefit in the first place from anti-myotonia treatment are the ones who present clinical severe myotonia, because I assume they might have an important impact of their symptoms in their daily life." In Díaz Manera's experience, "if they have symptoms that are impacting the way how they do things in their daily life, then they will benefit."

EXPERT DISCUSSION ON MEXILETINE DATA

In the second part of this interview series, the experts discussed the key clinical studies that provided the evidence to support the use of mexiletine in treating myotonia symptoms in patients with NDM.

Clinical data have shown that the symptoms of myotonia are reduced significantly following treatment with mexiletine, and the experts agreed that this has important implications for patients with NDM in terms of improvement in their QoL.[2,5,6] "There is actually very good evidence that treating patients who have NDM with mexiletine improves their symptoms," remarked Jayaseelan, "and this is really reflected in their QoL measures in the study and when you speak to the patients." Schneider-Gold agreed: "Patients with NDM can expect that mexiletine contributes to their QoL and their ability to move and to do all the things in daily life during the time they take mexiletine, and it has been clearly shown in short-term as well as in long-term studies there was no decline of efficacy of mexiletine during the treatment period."

Supporting the positive impact of mexiletine on both clinical symptoms and patient QoL, the experts referred to the randomised, placebo-controlled trial conducted in seven clinical centres in four countries[7] and also reported by Statland et al.[2] in 2012, as well as the more recent MYOMEX study[5] from France, which was reported in 2021. "Statland et al. showed significant improvements not only in the stiffness, but also in pain and fatigue scores for those patients who got mexiletine over placebo," stated Jayaseelan. "The MYOMEX study as well also showed significant improvement of QoL scores across the board for all domains." As Vicart elaborated: "According to the French MYOMEX study, in addition to the stiffness improvement, an improvement in QoL assessed by the INQoL scale was observed in patients with myotonia congenita and paramyotonia congenita, and this improvement under mexiletine was significant for the total population with the treatment effect on each domain of the INQoL questionnaires." Díaz Manera described several examples of mexiletine's clear (positive) impact on daily activities of patients, corroborating the findings in clinical trials that "patients explain that there is a clear change in the daily activities, thanks to the medication." Jayaseelan concluded: "So, I do think there's good evidence that mexiletine improves quality of life in patients."

When asked about long-term safety data supporting the prolonged use of mexiletine in patients with NDM, the medical experts highlighted the favourable safety profile and good tolerability of mexiletine. "There are short-term and long-term studies showing that there is no severe increase of side effects during treatment [...] mexiletine seems to be rather safe and well tolerated in most patients," commented Schneider-Gold. Vicart further explained that the long-term safety of mexiletine in NDM has been evaluated in two retrospective studies, which found that "no patient developed a cardiac arrhythmia or other serious side effects requiring drug discontinuation," and in which "mexiletine was considered as a well-tolerated drug in most of the patients."[8,9] Jayaseelan added that "in our clinical practice, we've not seen any severe cardiac adverse events [...] generally, the feeling is the long-term safety data does support prolonged use of mexiletine and that it's safe." This point was reiterated by Sansone: "There's real-world evidence and personal experience with years and years of mexiletine, meaning decades of use, with safety monitoring of both the symptoms and the ECG, with basically very few patients having to stop because of cardiac side effects."

All five experts in the neuromuscular field acknowledged that it would be helpful to continue to gather longer-term clinical safety data on the use of mexiletine in NDM, including in paediatric patients, as this will add to the existing clinical evidence base. "There is quite good safety data available on mexiletine in the short term, there's less long-term safety data," conceded Jayaseelan. "Long-term data would really be helpful, especially for the cardiac side and for gastrointestinal issues," added Sansone. Díaz Manera added that "although [mexiletine] is an anti-arrhythmia drug, there are no data suggesting that [it] has any cardiac toxic effects, which I think it's very important that patients do not develop arrhythmias because of the treatment."

All the experts were aligned on the view that mexiletine shows similar efficacy in patients with NDM, irrespective of the underlying channelopathy. "Based on the data and clinical studies, there's no major difference in the response to mexiletine in sodium and chloride channelopathies," commented Schneider-Gold. Vicart concurred: "None of the clinical trials published can conclude clearly to a significant difference of mexiletine efficacy between patients with chloride or sodium channel mutations." However, the medical experts explained that some adjustments may be required to the mexiletine dose in sodium channelopathy patients in the clinical practice setting, depending on the improvement in key symptoms such as pain. Jayaseelan pointed out that recessive patients can be more treatment resistant and may require higher doses of mexiletine to optimise clinical outcomes.

General consensus among the medical experts was that mexiletine data obtained from clinical trials showed good concordance and correlation with their real-life experiences of using the drug to treat patients with NDM. "Data from clinical studies really fit very well with real-life data, showing that mexiletine improves pain, myotonia, and, in some aspects, also weakness and fatigue, in patients with NDM," noted Schneider-Gold. "In both groups, sodium channelopathies and chloride channelopathies, there's no major difference and the effects are comparable in those types of NDM." This point was echoed by Jayaseelan: "We do see in clinical practice that patients notice quite striking differences in their stiffness when they start mexiletine [...] the real-life data very much reflects what we've seen in the trials," and further supported by Vicart, who stated: "In my opinion, the data from all the clinical trials, published for 10 years, now position mexiletine as the first treatment, [and] have such a strong evidence based on efficacy and safety." While Sansone agreed that "there's sufficient data to say that myotonia is taken care of by mexiletine," they added the caveat is "the extent of what symptoms really respond and for how long and for which patients specifically, I don't think there's sufficient information to be so clear on this." Sansone also noted that, in their experience, improvement in symptoms tended to be more marked in chloride versus sodium channel patients. Díaz Manera described their experience, and that "what patient say in the trial is what we see when we treat a patient in normal clinic, so patients improve their QoL [and] the daily life activities actually improve."

HOW EXPERTS ADDRESS PATIENT CONCERNS AND EXPECTATIONS ABOUT TREATMENT

For the third segment of the interview, the medical experts considered how to address patient concerns and expectations around treatment with mexiletine, particularly regarding safety, including cardiac assessments and follow-up.

The experts acknowledged that patient expectations before receiving mexiletine could have a significant influence on their treatment satisfaction. Vicart explained that "if a patient expects to be totally cured by mexiletine," then this patient has "a huge risk to be disappointed and then to stop the medication." Managing patients' expectations of potential improvements in their NDM symptoms was, therefore, seen as crucial when recommending mexiletine. "We go through quite a careful process

when we're prescribing mexiletine, or suggesting the treatment with mexiletine," elaborated Jayaseelan. "We do spend a lot of time explaining what we think will benefit from the mexiletine, so we talk about how it's going to most likely to benefit their stiffness, and possibly some of their pain and tiredness, but much more the stiffness, so we manage the expectations of what exactly the treatment is going to do for their non-dystrophic myotonia." Schneider-Gold agreed: "Depending on the severity of NDM, I explain that the patient will have benefit from mexiletine, but in some cases, it cannot be expected that the patient will be completely free of symptoms." Sansone mentioned that some patients may feel that myotonia is not really important to them "because of the warm-up phenomenon." Sansone shared their pragmatic approach to prompting those patients to think what their life would be like if they didn't have that problem, which usually results in them agreeing that it would be much better without myotonia. "Once they have the drug and they see it's really doing something, they rather would stay on the drug because they see it's working."

The experts in the neuromuscular field agreed on the importance of accurately positioning the benefits and risks of mexiletine when discussing treatment with patients with NDM. Jayaseelan said that they would begin by outlining the efficacy benefits of mexiletine to patients and then move on to an open discussion about the potential side effects and how these will be monitored, thus making it "much more likely that they get good benefit without having significant disadvantages from it."

Regarding potential side effects with mexiletine, Sansone noted: "My experience is that it's quite a well-tolerated drug." Sansone added that taking the drug with meals can help reduce the likelihood of gastrointestinal disturbances. Schneider-Gold concurred: "I tell the patient that no drug is really without outside effects and that he or she can't expect there will be no sensation of anything, but in normal situations, there will be no major side effects." Vicart reiterated that the benefit-to-risk balance for mexiletine is mainly favourable as "all the studies published showed that mexiletine significantly improved stiffness and, when it was assessed, the QoL, and that treatment was well tolerated, confirming a positive safety profile." In Díaz Manera's experience, patients with whom they discussed mexiletine "are not really worried about the adverse effects," and "when you do describe to them that they can improve, they are more interested in the positive part of the treatment than any potential harm."

Mexiletine requires mandatory cardiac assessments before initiation and during titration. The neuromuscular experts underscored the importance of good patient education to mitigate any potential impact of this on willingness to accept treatment. As Vicart advised: "It's our role to explain to the patient that there is no cardiac involvement in NDM and that in the literature data, older literature data showed the absence of any significant change in cardiac monitoring and assessment, or showed the absence of serious cardiac adverse events during short-term and long-term follow-up." However, Vicart acknowledged that "it's important to identify the patients who can have a potential underlying cardiac problem due to another origin and which can be aggravated by the mexiletine." Jayaseelan also pointed out that "most patients are very keen to have those initial tests done to make sure their heart is safe to have the medication [...] and most patients continue with them throughout and without significant problems." Díaz Manera explained that it is normal for patients to initially feel anxious about starting a treatment that "can be somewhat dangerous." Díaz Manera's recommendation to address these concerns was to discuss the long-term safety data, and to show patients that there is a clear plan to minimise risk, including the tests that will be performed. Sansone noted: "For all patients with myotonia, I think that a cardiac check to start with, with an ECG and a cardiologist saying okay you can start, makes everybody happy. And I don't see that as a limitation."

WHAT CAN BE LEARNT FROM THE CLINICAL DATA IN RELATION TO THE CARDIAC SAFETY OF MEXILETINE?

To further understand the experts' experience related to the cardiac safety profile of mexiletine, this topic was the focus of the final interview segment, with additional expert insights provided by Consultant Cardiologist Karim Wahbi, Cochin Hospital, Cardiology department, Paris, France.

"Mexiletine treatment [...] has a direct effect on the cardiac electrical system, and inappropriate use of the treatment can result in an increased risk for cardiac complications, mainly cardiac arrhythmias," clarified Wahbi. The other experts agreed that the paradoxical potential of mexiletine to cause or exacerbate arrhythmias was the main cardiac safety concern associated with the drug. However, Sansone pointed out that "patients with channelopathies usually do not have a cardiac rhythm abnormality as part of their disease." Sansone added that ECG monitoring is preferred, especially for patients with sodium channelopathies.

When asked about the long-term cardiac safety data supporting the use of mexiletine in patients with NDM, Wahbi responded: "Well, we have several studies showing that the safety of mexiletine in patients with NDM is extremely good. In those studies, which have been published to date, the incidence of major complication was extremely low." Wahbi concluded that "we have currently a body of evidence suggesting that the treatment can be used extremely safely in this population." Other experts and clinical studies support this view that the long-term data from clinical trials of mexiletine in NDM have not revealed any evidence of arrhythmia or increased risk of cardiac events during treatment.[8,9]

Key measures are already in place and outlined in the summary of product characteristic, to minimise the risk of potential cardiac side effects due to mexiletine in patients with NDM. The experts flagged the importance of implementing these precautionary steps, particularly in patients with pre-existing cardiac abnormalities. "It is extremely important to offer patients very careful cardiac assessments before the initiation of the treatment, just to make sure that there is no contraindication to the treatment and during follow up [...] as long as patients are treated," explained Wahbi. Wahbi continued: "Before the initiation of the treatment, it's important to have an ECG and an echocardiogram to make sure that patients do not have conduction defects, or repolarisation abnormalities, or left ventricular dysfunction that may present a contraindication to the treatment [...] Later, patients treated with mexiletine should have cardiac investigations [...] at least every 2 years, if all previous assessments were normal, and those assessments should be repeated more frequently, every 6 months or on a yearly basis, if mild abnormalities have been identified, that do not present contraindications to use the treatment. Those assessments should include an ECG [at each follow-up visit and less frequently], an echocardiogram and a Holter ECG." These recommendations were supported by Vicart: "Patients who can have another pre-existing cardiac abnormality, those patients will need cautious cardiac monitoring with ECG performed after each dose increases and a periodic cardiac evaluation at least annually, and for the other patient without pre-existing cardiac abnormalities, which fortunately represent the majority of the patients with NDM, a periodic ECG is recommended annually or at least every 2 or 3 years."

Wahbi advised that "one other important point is that patients who complain of cardiac symptoms during follow-up systematically referred to a cardiologist in order to estimate the potential role played by mexiletine in the development of those symptoms, and to make sure that patients did not develop significant cardiac abnormalities during follow-up."

The experts then discussed the potential benefits of the mandatory cardiac assessments required before initiation and during titration of mexiletine in patients with NDM, noting how these steps can

help both patients and clinicians feel 'safer' in prescribing mexiletine by ensuring any cardiac risks are effectively mitigated. As Wahbi emphasised: "The purpose of cardiac investigations is to avoid major cardiac complications in patients treated with mexiletine. If mexiletine is used properly, then the cardiac risk is close to that of an individual in the general population. So, it's very important to arrange cardiac investigations, just to make sure that patients do not have abnormalities that may confer a specific risk for them to develop cardiac complications [...] if you do those assessments properly, then patients have very reasonable risk to develop complications and the treatment can be used really safely." Overall, the experts concurred that the cardiac safety profile of mexiletine in patients with NDM is equivalent to that in a healthy, or control, population when the drug is used as directed.

In summary, the NDM experts agreed that there was a strong link between how physicians present treatment options, such as mexiletine, and how patients perceive the benefits of treatment. For patients with chronic diseases, such as NDM, an improved understanding of the burden of disease and benefits of treatment can improve drug treatment compliance and treatment outcomes, leading to greater success in controlling symptoms such as myotonia.

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