

# Expert insights: A Delphi-driven neurologists' panel: real-world mexiletine use in patients with myotonic disorders in Italy

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## Introduction

- Myotonic disorders – such as non-dystrophic myotonias (NDMs) and myotonic dystrophies (DMs) – are a heterogeneous group of debilitating genetic conditions, characterised by a delay in muscle relaxation after a contraction stimulus.<sup>1</sup>
- Myotonia places a substantial burden on the daily quality-of-life (QoL) of those affected, particularly as there is no curative or genetic treatment available.<sup>2,5</sup> – Presently, symptomatic treatment for myotonia is the only approved option.
- Mexiletine is the only pharmacological agent currently approved for treating adults with NDM and it is considered as the first-line agent.<sup>6,9</sup>
- There is general consensus that protocols to treat myotonia need to be implemented, to provide the best support for people living with NDM and DM.
- However, due to production issues, the availability of locally-produced mexiletine to patients in Italy was compromised in 2022.<sup>10</sup>

## Objective

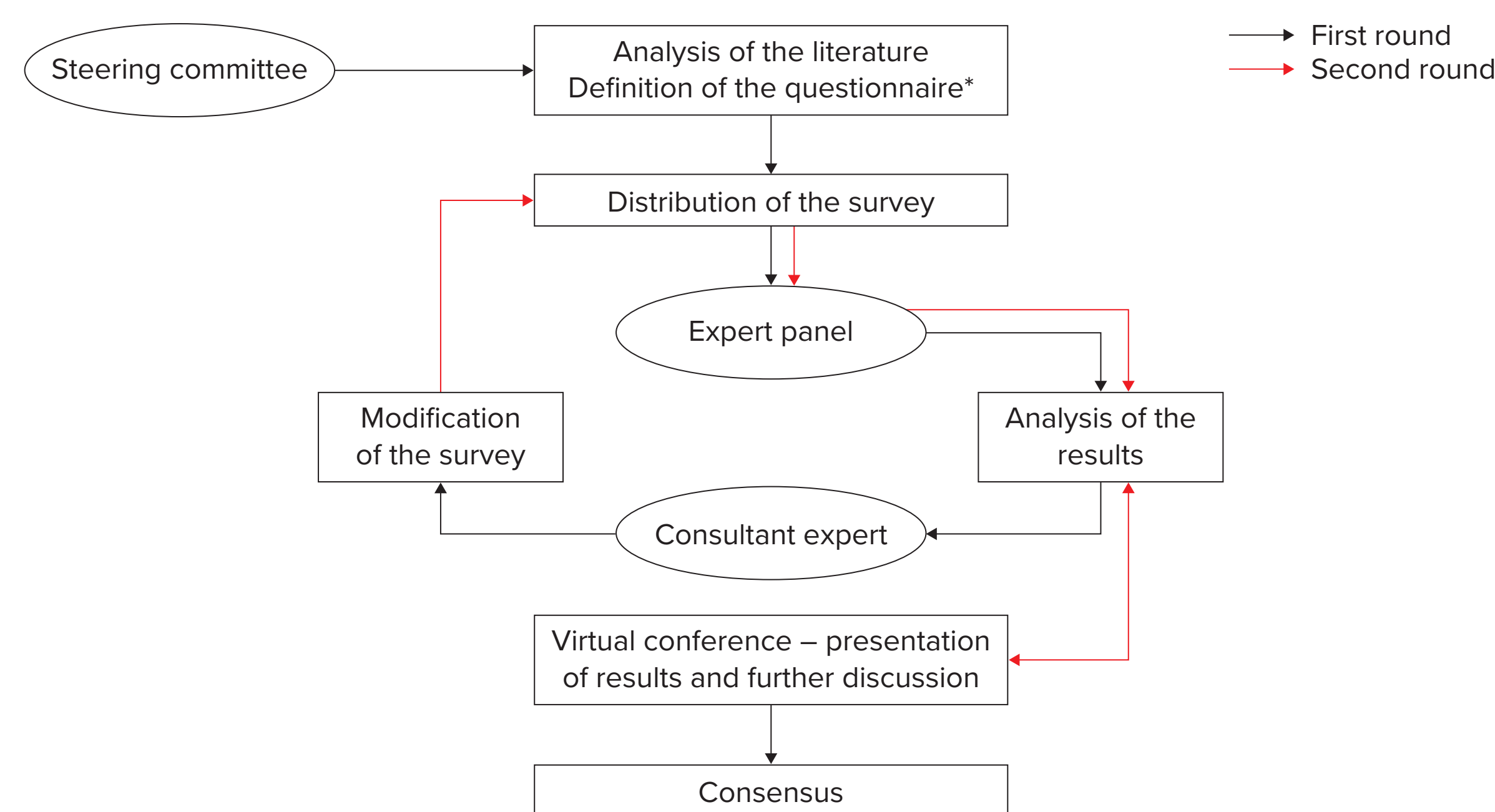
- To analyse current mexiletine use in Italian clinical practice, based on expert input from a panel of eight Italian Neurologists who took part in a two-round Delphi panel between June and October 2022.

## Methods

### Delphi process

- The Delphi process is a structured iterative survey, in which, during each round, experts express their opinions anonymously (Figure 1).
- These expert responses are collected, analysed and re-proposed to the panel during the next round.
- There then follows a virtual conference to discuss the results with the aim of building a consensus among panellists.

Figure 1. Design of the Delphi consensus process



\*The Clinical Expert was part of the Steering Committee.

### Selection of the expert panellists

- Eight Italian neurologists were selected based on the following criteria:
  - Working at a main Italian neuroscience specialist centre with  $\geq 5$  NDM and/or  $\geq 15$  DM patients (quantifiable expertise);
  - Recognised neurology expert in the treatment of myotonia (qualitative expertise).

### Questionnaire design

- The questionnaire was developed by a steering committee including the Pharmalex and Lupin teams, and a key clinical expert.
- The questionnaire included the following topics:
  - Overall experience in the clinical management of patients;
  - Snapshot of mexiletine prescribing;
  - Impact of mexiletine use on clinical and QoL outcomes;
  - Access to mexiletine;
  - Current status of mexiletine use in Italian clinical practice.

### Data analysis

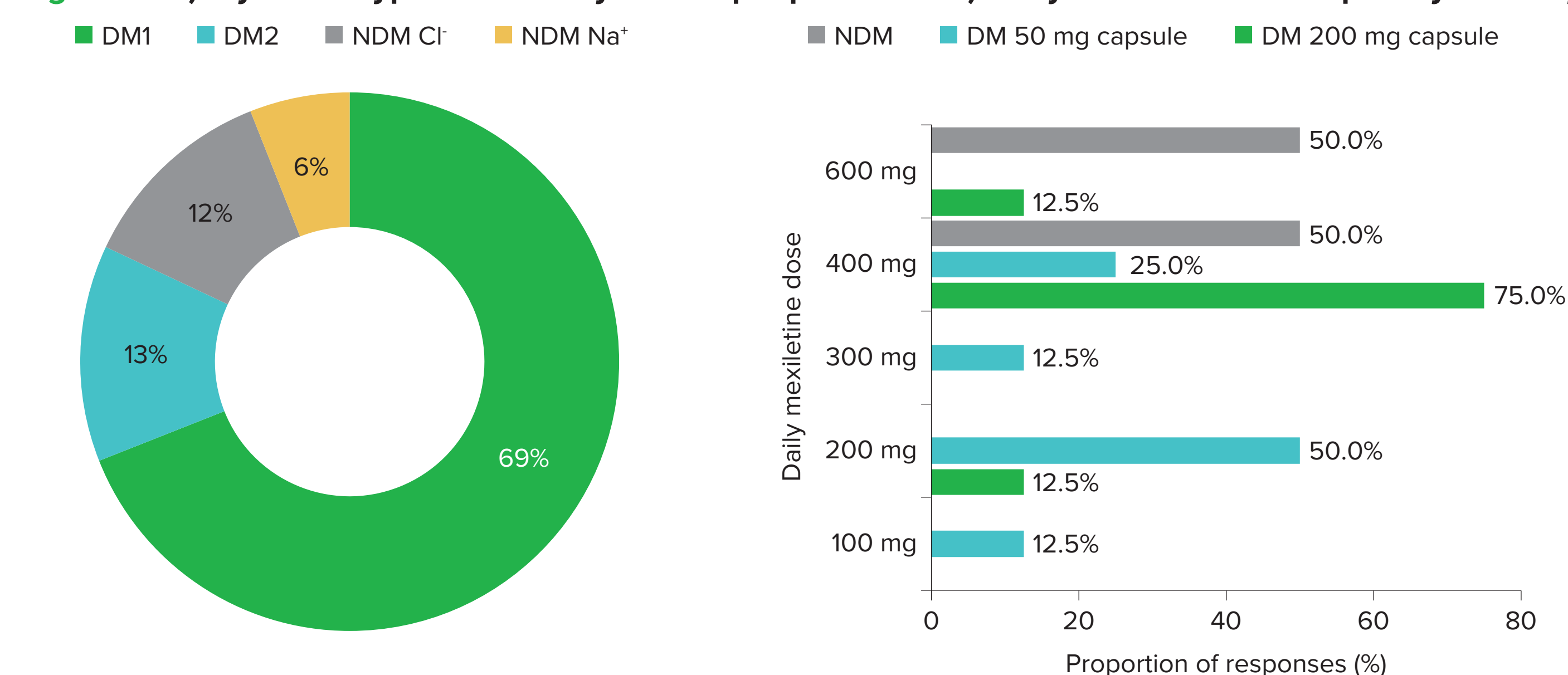
- Results are expressed as percentages of responses for all of the closed questions, by topic.

## Results

### Experience in clinical use of mexiletine

- The majority of patients under the care of Delphi panellists had DM1 (Figure 2A).
- As expected, people with NDM were receiving 400 mg (50%) or 600 mg (50%) of mexiletine daily
- Mexiletine doses for people with DM were more variable, particularly for those receiving multiples of the 50 mg capsule, rather than the 200 mg, capsule (Figure 2B).

Figure 2. A) Myotonia types treated by the Delphi panellists B) Daily mexiletine doses per myotonia type



Na<sup>+</sup>, sodium channelopathy; Cl, chloride channelopathy; DM, dystrophic myotonia; NDM, non-dystrophic myotonia.

### Snapshot of mexiletine prescribing

- Key factors supporting mexiletine treatment in NDM and DM: symptom severity; genetically confirmed disease; current mexiletine treatment; symptoms being relevant for patients of any age; drug-naïve patient; normal cardiac findings (Table 1).
- The key factor that would affect mexiletine prescribing was the availability and reimbursement of mexiletine through the Italian National Health Service.

## Conclusions

- Mexiletine treatment has a well-recognised role in reducing the symptomatic burden for people with NDM or DM;<sup>11</sup> this view was affirmed by the expert Delphi panellists, based on current clinical practice in Italy.
- From the panellists' experiences, the mexiletine 50 mg capsule formulation was associated with the greatest variability in daily dosing.
- There was overall accord on the symptoms and clinical factors that would prompt mexiletine treatment.
- Reimbursement for mexiletine treatment by the Italian NHS was considered the key factor in facilitating prescribing.
- The panel agreed on several measures that would best quantify the effectiveness and impact on QoL with mexiletine.
- Patient management and treatment adherence could be improved by facilitating consistent access to mexiletine and developing new formulations that would ease administration.

Table 1. Agreement levels among Delphi panellists regarding factors affecting mexiletine treatment choice and prescription

Feature	% Delphi panellists agreement	
	NDM	DM1 and DM2
<b>Factors affecting treatment choice in favour of mexiletine</b>		
• Symptom severity affecting daily living	88	100
• Genetic confirmation	65	88
• Patient already receiving mexiletine	75	75
• Symptom judged to be relevant for a patient of any age	75	63
• Drug-naïve patient	75	75
• Normal ECG findings and cardiology approval	75	63
• Normal ECG findings, 24-hour ECG Holter monitoring, 2D echocardiograms and cardiology approval	50	63
• Patient already under another off-license treatment	38	50
• Other	13	25
<b>Factors affecting drug prescription</b>		
• Availability and deliverability of prescribed mexiletine regardless of Italian NHS reimbursement	13	13
• Only if availability and reimbursement of mexiletine occurs through the Italian NHS	88	88
• Other	25	25

DM, dystrophic myotonia; ECG, electrocardiogram; NDM, non-dystrophic myotonia; NHS, National Health Service.

### Evaluation of mexiletine clinical effectiveness and its influence on QoL

- The most impactful measures of the clinical effectiveness of mexiletine for NDM were considered to be Individualised Neuromuscular Quality of Life Questionnaire (INQoL) measures of muscle locking, ability to perform daily activities and pain (Table 2).
- For DM1, visual-analogue scores of stiffness/myotonia, pain or fatigue followed by handgrip myotonia and INQoL were considered to be the most impactful measures (data not shown).

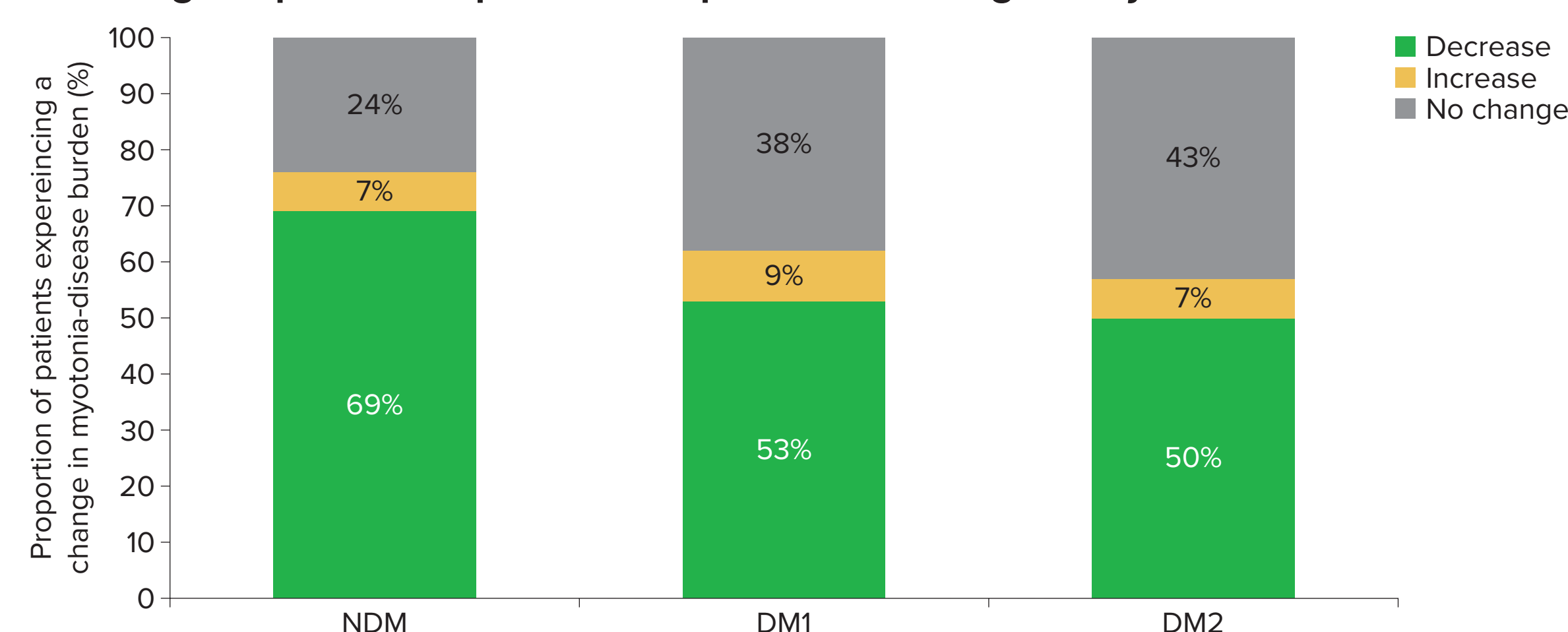
Table 2. Top 10 INQoL v1.2 domains that Delphi panellists considered to be most impactful for the management of myotonia using mexiletine in people with NDM

Ranking	INQoL item	Ranking	INQoL item
1	Muscle locking	6	Tiredness/fatigue
2	Daily activity	7	Muscle weakness
3	Pain	8	Emotional state/feelings
4	Leisure and work activity	9	Relationships
5	Independence	10	Body image/looks

INQoL, Individualised Neuromuscular Quality of Life Questionnaire.

- For NDM and DM1, a majority of the Delphi panellists indicated that mexiletine treatment would decrease myotonia symptoms compared with best supportive care (Figure 3).
- For DM2, half of the panellists thought that mexiletine would decrease myotonia symptoms.
- Across all three myotonic disorders, a minority of panellists ( $\leq 9\%$ ) indicated that mexiletine would increase myotonia symptoms compared with best supportive care.

Figure 3. Percentage of patients expected to experience a change in myotonia-disease burden



DM, dystrophic myotonia; NDM, non-dystrophic myotonia.

### Mexiletine prescription and access through the Italian Military supply

- Mexiletine was available from the Italian Military Chemical Pharmaceutical Plant, a public institution, between 2010–2022.
- Issues with this source of mexiletine included limited prescription length of 6 months (NDM and DM1) and 6.5 months (DM2) as well as delays in obtaining prescriptions (25% of the panel reported delays  $>14$  days). – These delays were considered to be due to difficulties faced by pharmacies in obtaining mexiletine (75%) or by physician-related delays (25%).
- Delphi panellists considered ease of administration (100%), reduction in time spent procuring the drug (100%), reimbursement by the Italian NHS (100%) and formulation that supports the correct dosage (50%) as key factors to improve patient compliance with this treatment.

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