Myotonic Dystrophy Health Index (MDHI): Measuring Patient-Reported Disease Burden

Myotonic Dystrophy Patient-Centered Therapy Development Workshop
9/17/15
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What is the MDHI

- Disease-Specific Patient-Reported Outcome Measure for myotonic dystrophy type-1
- Designed and validated to satisfy all FDA guidelines for drug labeling purposes
- Composed of 17 individual subscales that together measure multifactorial patient-reported burden of disease (NINDS Common Data Elements)
What is the MDHI

- Disease-Specific Patient Reported Outcome Measure for myotonic dystrophy type-1
- Designed and validated to satisfy all FDA guidelines for drug labeling purposes
- Composed of 17 individual subscales representing concepts that myotonic dystrophy patients have identified as having the greatest impact on their lives
What does the MDHI Measure?
(MDHI Subscales)

- Mobility
- Upper Extremity Function
- Ability to do Activities
- Fatigue
- Pain
- Gastrointestinal Health
- Vision
- Communication
- Hearing
- Sleep
- Emotional Health
- Cognition
- Social Satisfaction
- Social Performance
- Myotonia
- Respiratory Function
- Swallowing
- Multifactorial Patient-Reported Burden of Disease
Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical
<table>
<thead>
<tr>
<th>Measurement Property</th>
<th>Type</th>
<th>What Is Assessed</th>
<th>FDA Review Considerations</th>
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| **Reliability**                  | Test-retest or intra-interviewer reliability   | Stability of scores over time when no change is expected in the concept of interest | • Intraclass correlation coefficient  
• Time period of assessment                                                              |
|                                 | (for interviewer-administered PROs only)      |                                                                                 |                                                                                           |
| Internal consistency             |                                                 | • Extent to which items comprising a scale measure the same concept            | • Cronbach’s alpha for summary scores  
• Intercorrelation of items that contribute to a score  
• Internal consistency                                                           |
| Inter-interviewer reliability    | Agreement among responses when the PRO is       |                                                                                 | • Interclass correlation coefficient                                                      |
|                                 | (for interviewer-administered PROs only)      | administered by two or more different interviewers                           |                                                                                           |
| Validity                         | Content validity                               | Evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity. | • Derivation of all items  
• Qualitative interview schedule  
• Interview or focus group transcripts  
• Items derived from the transcripts  
• Composition of patients used to develop content  
• Cognitive interview transcripts to evaluate patient understanding |
|                                 | Construct validity                              | Evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient groups. | • Strength of correlation testing *a priori* hypotheses (discriminant and convergent validity)  
• Degree to which the PRO instrument can distinguish among groups hypothesized *a priori* to be different (known groups validity) |
| Ability to detect change         | Evidence that a PRO instrument can identify differences in scores over time in individuals or groups (similar to those in the clinical trials) who have changed with respect to the measurement concept | • Within person change over time  
• Effect size statistic                                                              |                                                                                           |
Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1)

ABSTRACT

Objective: To determine the most critical symptoms in a national myotonic dystrophy type 1 (DM1) population and to identify the modifying factors that have the greatest effect on the severity of these symptoms.

Methods: We performed a cross-sectional study of 278 adult patients with DM1 from the national registry of patients with DM1 between April and August 2010. We assessed the prevalence and relative significance of 221 critical DM1 symptoms and 14 disease themes. These symptoms and themes were chosen for evaluation based on prior interviews with patients with DM1. Responses were categorized by age, CTG repeat length, gender, and duration of symptoms.

Results: Participants with DM1 provided symptom rating survey responses to address the relative frequency and importance of each DM1 symptom. The symptomatic themes with the highest prevalence in DM1 were problems with hands or arms (93.5%), fatigue (90.8%), myotonia (90.3%), and impaired sleep or daytime sleepiness (87.9%). Participants identified fatigue and limitations in mobility as the symptomatic themes that have the greatest effect on their lives. We found an association between age and the average prevalence of all themes (p < 0.01) and between CTG repeat length and the average effect of all symptomatic themes on participant lives (p < 0.01).

Conclusions: There is a wide range of symptoms that significantly affect the lives of patients with DM1. These symptoms, some previously underrecognized, have varying levels of importance in the DM1 population and are nonlinearly dependent on patient age and CTG repeat length. Neurology® 2012;79:1-1

GLOSSARY

- DM1 = myotonic dystrophy type 1
- FDA = Food and Drug Administration
- FSHD = facioscapulohumeral muscular dystrophy
- PRISM-1 = Patient Reported Impact of Symptoms in Myotonic Dystrophy Type 1
Phase 1: DM1 Interviews

Themes
- Limitations with mobility and walking
- Problems with hands and arms
- Activity impairment
- Emotional issues
- Cognitive impairment
- Social role limitation
- Social role dissatisfaction
- Gastrointestinal dysfunction
- Sleep disturbance
- Fatigue
- Pain
- Communication difficulties
- Vision hearing or smell
- Myotonia

Domains
- Physical health
- Mental health
- Social health

Phase 2: National Cross-Sectional Validation Study

- Prevalence of themes and symptoms in DM1
- Relative importance of themes and symptoms in DM1
- Relationships of the frequency and importance of DM1 themes and symptoms to patient age, gender, CTG repeat length, and duration of symptoms

Source
- 20 Patient interviews
- 1165 Direct quotes

221 Symptoms
The myotonic dystrophy health index: Initial evaluation of a new outcome measure.


Author information

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Abstract

Introduction: In preparation for clinical trials we examine the validity, reliability, and patient understanding of the Myotonic Dystrophy Health Index (MDHI). Methods: Initially we partnered with 278 myotonic dystrophy type-1 (DM1) patients and identified the most relevant questions for the MDHI. Next, we used factor analysis, patient interviews, and test-retest reliability assessments to refine and evaluate the instrument. Lastly, we determined the capability of the MDHI to differentiate between known groups of DM1 participants. Results: Questions in the final MDHI represent 17 areas of DM1 health. The internal consistency was acceptable in all subscales. The MDHI had a high test-retest reliability (ICC=0.95) and differentiated between DM1 patient groups with different disease severities. Conclusion: Initial evaluation of the MDHI provides evidence that it is valid and reliable as an outcome measure for assessing patient-reported health. These results suggest that important aspects of DM1 health may be effectively measured using the MDHI. © 2013 Wiley Periodicals, Inc.
Figure e-1: Development of the MDHI

- Interviews With DM1 Patients, Clinicians, Researchers, and Family Members (PRISM-1)
  - Cross-sectional Study of 278 DM1 Patients (Group 1)
    - Expert Review
    - First Factor Analysis (Group 1)
    - Patient Interviews (Group 2)
  - Test-Retest Evaluation (Group 3)
  - Final Factor Analysis and Known Groups Testing (Group 1), and Final Test-Retest Reliability Testing (Group 3)

235 Symptom Questions 14 Themes
175 Symptom Questions 14 Themes
115 Symptom Questions 15 Themes
117 Symptom Questions 18 Themes
116 Symptom Questions 18 Themes

Final MDHI: 114 Symptom Questions 17 Themes

60 Questions Removed (Low Population Impact Score)
60 Questions Removed * 1 Theme and 1 Question Added
4 Themes Added, 1 Theme Removed, 2 Questions Added, 1 Question Removed, ** 12 questions moved to different thematic group
1 Question Removed, 6 Questions Reworded
2 Questions Removed 1 Theme Removed

* 31 questions excluded due to low responsiveness
15 questions excluded due to vague wording
6 questions excluded due to redundancy
5 questions excluded due to being potentially offensive
2 questions excluded due to being tied to affluence
1 question excluded due to wording requiring a high vocabulary

**New Themes: 1) Breathing Difficulties; 2) Choking or Swallowing Issues; 3) Problems with Vision; 4) Hearing Difficulties
Removed theme/question: Problems with Vision, Hearing, or Smell
New Questions: 1) Problems with Vision; 2) Choking and Swallowing Issues

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Figure 1: The Test-Retest Reliability of the MDHI

ICC=0.95
<table>
<thead>
<tr>
<th>MDHI Subscales</th>
<th>Number of Questions in Final Subscale</th>
<th>Intraclass Correlation Coefficient (ICC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.) Mobility</td>
<td>13</td>
<td>0.91</td>
</tr>
<tr>
<td>b.) Upper Extremity Function</td>
<td>11</td>
<td>0.92</td>
</tr>
<tr>
<td>c.) Ability to do Activities</td>
<td>14</td>
<td>0.94</td>
</tr>
<tr>
<td>d.) Fatigue</td>
<td>4</td>
<td>0.94</td>
</tr>
<tr>
<td>e.) Pain</td>
<td>8</td>
<td>0.88</td>
</tr>
<tr>
<td>f.) Gastrointestinal Issues</td>
<td>6</td>
<td>0.91</td>
</tr>
<tr>
<td>g.) Vision</td>
<td>4</td>
<td>0.89</td>
</tr>
<tr>
<td>h.) Communication</td>
<td>7</td>
<td>0.87</td>
</tr>
<tr>
<td>i.) Sleep</td>
<td>4</td>
<td>0.76</td>
</tr>
<tr>
<td>j.) Emotional Issues</td>
<td>12</td>
<td>0.91</td>
</tr>
<tr>
<td>k.) Cognitive Impairment</td>
<td>9</td>
<td>0.90</td>
</tr>
<tr>
<td>l.) Social Satisfaction</td>
<td>6</td>
<td>0.97</td>
</tr>
<tr>
<td>m.) Social Performance</td>
<td>7</td>
<td>0.92</td>
</tr>
<tr>
<td>n.) Myotonia</td>
<td>4</td>
<td>0.69</td>
</tr>
<tr>
<td>o.) Breathing</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>p.) Swallowing</td>
<td>3</td>
<td>0.81</td>
</tr>
<tr>
<td>q.) Hearing</td>
<td>1</td>
<td>0.97</td>
</tr>
</tbody>
</table>
## MDHI Question Distribution: Internal Consistency (17 Subscales)

<table>
<thead>
<tr>
<th>DM1 Specific Subscales</th>
<th>Number of Questions in Subscale (total= 114)</th>
<th>Internal consistency (Cronbach’s alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.) Limitations with your mobility or walking</td>
<td>13</td>
<td>0.977</td>
</tr>
<tr>
<td>b.) Problems with your hands or arms</td>
<td>11</td>
<td>0.941</td>
</tr>
<tr>
<td>c.) Inability to do activities</td>
<td>14</td>
<td>0.949</td>
</tr>
<tr>
<td>d.) Fatigue</td>
<td>4</td>
<td>0.940</td>
</tr>
<tr>
<td>e.) Pain</td>
<td>8</td>
<td>0.933</td>
</tr>
<tr>
<td>f.) Gastrointestinal issues</td>
<td>6</td>
<td>0.849</td>
</tr>
<tr>
<td>g.) Problems with your vision</td>
<td>4</td>
<td>0.816</td>
</tr>
<tr>
<td>h.) Communication difficulties</td>
<td>7</td>
<td>0.889</td>
</tr>
<tr>
<td>i.) Impaired sleep or daytime sleepiness</td>
<td>4</td>
<td>0.837</td>
</tr>
<tr>
<td>j.) Emotional issues</td>
<td>12</td>
<td>0.933</td>
</tr>
<tr>
<td>k.) Difficulty thinking</td>
<td>9</td>
<td>0.910</td>
</tr>
<tr>
<td>l.) Decreased satisfaction in social situations</td>
<td>6</td>
<td>0.854</td>
</tr>
<tr>
<td>m.) Decreased performance in social situations</td>
<td>7</td>
<td>0.903</td>
</tr>
<tr>
<td>n.) Myotonia</td>
<td>4</td>
<td>0.874</td>
</tr>
<tr>
<td>o.) Breathing difficulties</td>
<td>1</td>
<td>n/a</td>
</tr>
<tr>
<td>p.) Choking or swallowing issues</td>
<td>3</td>
<td>0.758</td>
</tr>
<tr>
<td>q.) Hearing difficulties</td>
<td>1</td>
<td>n/a</td>
</tr>
</tbody>
</table>
MDHI Total Score by Known Groups

- Employed (Blue: Yes/Red: No)
- CTG Repeat Status (Blue: <300/Red: ≥300)
- Education (Blue: College or Advanced Degree/Red: No College Degree)
- Duration of Symptoms (Blue: ≤20/Red: >20 years)

Mean MDHI Total Score
MDHI Subscale Scores by Employment Status

(p-value <0.02 except for l. and p.)
COMFORT Study (Construct and Convergent Validity)

- Comparison of MDHI with Functional and Other Research Testing (COMFORT)
- A cross-sectional study of DM1 patients comparing MDHI scores to 25 functional tests, six laboratory tests, 18 generic patient reported outcome assessments, and seven physician assessments
- Completed as part of our: Study of Pathogenesis and Progression in Dystrophia Myotonica (STOOPP DM) Wellstone study
Conclusion

- The MDHI is a disease-specific, valid, responsive, and reliable instrument designed to optimally measure patient-reported disease-burden during clinical trials.
Thank You

- Nicholas Johnson, MD
- Richard Moxley, MD
- Robert Holloway, MD, MPH
- Charles Thornton, MD
- Robert Griggs, MD
- James Hilbert, MS
- Tracy Forrester
- Liz Luebbe
- Bill Martens, BA
- Mike McDermott, Ph.D.
- Nancy Chin, Ph.D.
- Eileen Eastwood
- Jeanne Dekdebrun
- David Herrmann, M.B.B.Ch.
- Shree Pandya, PT, MS
- Kate Eichinger, PT, DPT, NCS
- Deb Guntrum, NP
- Cindy Gibson, NP
- Barbara Vickrey, MD (U.C.L.A.)
- David Cella, Ph.D. (PROMIS Network)
- Nan Rothrock, Ph.D (Northwestern, IL)
- Rita Bode, Ph.D. (PROMIS Network)
- David Victorson, Ph.D. (NeuroQol Network)
- Ora Prilleltensky, Ed.D. (University of Miami)
- John Day, M.D., Ph.D. (Stanford, California)
- John Kissel, M.D. (The Ohio State, Ohio)
- Kevin Flanigan, M.D. (Nationwide Children’s, Ohio)
- Kenneth Fischbeck, M.D. (NIH)
- Tatiana Foroud, Ph.D. (Indiana University, Indiana)
- Giovanni Meola, MD (Milan, Italy)
- Baziel Van Engelen, MD, Ph.D. (Nijmegen, Netherlands)
- Benedikt Schoser, MD (Munich, Germany)
- Silvere van de Maareel, Ph.D. (University of Leiden)
- Richard Lemmers, Ph.D. (University of Leiden)
- Michael Rose, M.D. (Kings College, United Kingdom)
- Craig Campbell, M.D. (University of Western Ontario, Canada)
- Anne-Berit Ekstroem, MD, PhD (Queen Silvia Children’s Hospital, Sweden)