Measuring Clinical Treatment Response in Myasthenia Gravis

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KEYWORDS

• Myasthenia gravis • Outcome measurement • Responsiveness
• Minimal important difference • Disability

KEY POINTS

- Newer outcome measures incorporate more input from patients and have undergone more rigorous psychometric analysis.
- Ideal measures in clinical care are brief to administer, whereas in clinical trials more comprehensive and overlapping measures are needed to demonstrate a positive effect.
- Minimal clinically important differences are available in very few of the outcome measures but can help to inform clinical trial design and sample size estimation.

INTRODUCTION TO HEALTH-RELATED OUTCOME MEASURES

There are several aspects of health that can be measured, and these represent different aspects of the disease, from the pathophysiology (eg, antibody titers), to the symptoms

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and signs, to the effect on the individual and their relation to society.[1] Because different outcome measures are aimed at different aspects of the disease process, it is fundamental to understand what a given tool measures, as well as for which purpose it was developed and in which population it was tested. One way to understand these different aspects of the disease is through the International Classification of Functioning, Disability and Health (ICF),[2] published by the World Health Organization. The ICF identifies 3 major ways in which a disease or injury affects in individual: impairments of body function or structures, which are basically the signs and symptoms; activity limitations, which are the effects of the disease and its symptoms on activities of daily life; and participation limitations, which are the effects on a patient's social interactions, such as looking for work or caring for their family. Additionally, these aspects of the disease are also affected by personal and environmental factors (eg, social support, cultural factors, and accessibility). Disability is—according to the ICF—the interaction between symptoms, activities, and participation restrictions and personal and environmental factors.[2] Health-related quality of life (HRQoL) goes beyond the concept of disability and it is, by definition, a subjective and multidimensional concept, including physical functioning, mental or psychological well-being, occupational status, and social interactions.[3] The impairments of body functions/structures are thought to be less affected by social and environmental factors and, therefore, are typically considered to reflect more directly disease severity. This factor is why most outcome measures aimed at quantifying disease severity capture the signs and symptoms, whereas measures focused on the impact of the symptoms on the individual as a whole are usually disability or HRQoL measures. Putting these concepts into the perspective of a clinical trial, the primary outcome should match the study intervention. For example, a phase II study for a new medication will likely be focused on the effect of signs and symptoms, whereas a psychosocial intervention will probably have more effect on HRQoL or disability than on the symptoms in isolation. **Fig. 1** depicts the ICF model in relation to some of the outcome measures specific to myasthenia gravis (MG) that are available.

Additionally, when choosing an outcome measure, it is fundamental to recognize that, beyond what they measure, they might have been developed with different purposes, typically discriminative, predictive, and evaluative.[4] Discriminative means that a measure can distinguish between individuals that have different degrees of the underlying construct (eg, more or less severe disease). Predictive measures are aimed at classifying individuals such as in a diagnostic test or predicting an outcome. Finally, evaluative measures are aimed at detecting change, which is fundamental to determining treatment response. Additionally, there are several methodologic requirements that need to be met to ensure that the measure is adequate for the intended purpose. All measures have to be valid (ie, measure what they are supposed to measure) and reliable (ie, reproducible). In addition, evaluative measures have to demonstrate responsiveness, or the ability to detect change. To interpret change scores, it is important to know the minimal important difference (MID), which is the smallest change in a measure that is meaningful for patients.[5] Additionally, there has been a shift in recent years toward more patient-reported outcomes, considering that patients are the best judges of their disease status and that many symptoms or signs might not be evident in a clinical encounter or—when present—do not affect patient function. The specific standards for the development of outcome measures are beyond the scope of this article, but for those interested, the US Food and Drug Administration[6] and the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)[7] guidelines are excellent resources. Finally, it is important to keep in mind that validity, reliability, and responsiveness are not universal characteristics of a measure, and depend on the populations and interventions tested.[8]