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Letter to the Editor

Using modified Ashworth scale for assessing multiple sclerosis-associated spasticity: a high time for a paradigm shift

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The Phase 3 RELEASE MSS1 clinical trial (NCT04657666) investigated the effects of nabiximols oromucosal spray (marketed as Sativex® in 29 countries outside the United States) on the clinical measures of multiple sclerosis (MS) subjects with moderate to severe spasticity, who are not responsive to other anti-spasticity medications.[1] This study determined that this specific treatment did not meet the primary end-point of change (Lower Limb Muscle Tone-6 [LLMT-6]) as measured by the Modified Ashworth Scale (MAS). Failure to meet the primary defined outcome measure might reflect a lack of efficacy of therapy or insensitivity to the outcome measure chosen.

Clinically, spasticity is manifested as an involuntary activation (or relaxation failure) of muscle tissue as a result of an upper motor neuron syndrome. Spasticity is reported to impact 60% to 84% of people with MS (PwMS).[2] Recently, Fernández and his colleagues proposed a broad concept of 'Spasticity-Plus Syndrome', which includes the determination of spasticity and associated symptoms (i.e. pain, bladder dysfunction, and sleep alterations).[3] Although the appreciation of the impact of spasticity has evolved, the dilemma remains as to the optimal definition and measurements of spasticity from both patient and clinician perspectives.[1] Ambiguity in both definition and measurement sensitivity impacts scale sensitivity and validity. Hence the reason that the MAS, despite its wide use, is also widely criticized as an ineffective assessment scale.[2,4,5] There are multiple factors contributing to this dilemma and limitations in this scale including lack of comprehensive assessment, failure to include dynamic measurements of spasticity with change in position or movement, limited standardized protocol for interrater reliability/consistency, limited reliability that varies between limbs impacted, lack of sensitivity in defining and detecting variations in spasticity along a meaningful continuum, and non-inclusion of the patients perspective on spasticity impact and change.[2,4,5]

In the RELEASE MSS1 clinical trial, nabiximols oromucosal spray was not demonstrated to effectively reduce lower extremity spasticity as assessed in knee flexors and extensors, and plantar flexors by MAS.[1] This failure to demonstrate therapeutic efficacy is intriguing given the meta-analysis that concluded that both the inter-rater and intra-rater MAS was at best only fair to moderate for lower extremities but better for upper extremities.[6] It is therefore possible that the failure to achieve the primary outcome measure in this trial might not be due to therapy efficacy, but the failure of the sensitivity and reliability of the outcome measure itself. Nabiximols have been approved for the reduction of spasticity in 29 countries, and a recent review of nabiximol treatment of MS spasticity highlighted that the MAS is less patient-centric, more inconsistent, and insufficiently quantitative in the measurement of the degree or change in spasticity in PwMS.[5] Therefore, it is critical that new reliable quantitative sensitive measures are needed to assess spasticity in PwMS and gauge the real-world impact.

Despite the availability of several alternative quantitative tools to assess spasticity in PwMS, none are consistently utilized nor felt to be valid and reliable.[7] In this line, Balci[7] indicated that perhaps spasticity could potentially be better assessed by clinical examination augmented with biomechanical and/or electrophysiological measurements. This approach ideally would include

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the patient's perspective of impact and change. The use of newer methods or modification and enhancement of the existing scales by the inclusion of such complementary biomechanical (e.g. pendulum test, isokinetic dynamometer), neurophysiological, and/or other techniques are more reliable and sensitive.[7]

Notably, neurophysiological assessments like the Hoffmann reflex (H-reflex), the Stretch Reflex (SR), the H/M ratio, and the F/M ratio – recorded during active and functional movements – are the more promising and reliable complementary options to measure spasticity.[7] A study showed that the measurement of SR based on the use of non-robotic, surface electromyography exerted higher sensitivity and specificity than MAS and the numeric rating scale (NRS).[8] However, it is an exploratory observational study, and there is no placebo arm. Hence, more studies are required to advocate the use of SR as a standalone option for spasticity evaluation.

Carod-Artal and his colleagues indicated that the numerical rating scale for spasticity (NRS-S) might be more feasible than MAS due to the improved validity, and a patient-centric approach that can be easily included in routine care.[5] The Modified Tardieu Scale (MTS) has been reported to be reliable, valid, and superior to MAS for knee flexors and extensors, and ankle plantar flexors.[7] The Fugl-Meyer Assessment for the lower extremities (FMA-LE) is another alternative reliable spasticity evaluation scale based on 5 parameters (sensory and motor functions, pain, balance, and range of motion).[9] Other potential alternative measures of spasticity include the Multiple Sclerosis Spasticity Scale (MSSS88) and Patient-Reported Impact of Spasticity Measure (PRISM), which reliably assesses the impact of spasticity along daily life activities and social functions from the patient's perspective.[2,7] The Multiple Sclerosis Walking Scale (MSWS-12) and Multiple Sclerosis Impact Scale (MSIS-29) provide alternative measures to assess spasticity impact from the patient's perspective.[7]

To further refine measurements of spasticity and enhance the sensitivity and reliability of spasticity measurements, the incorporation of complementary technology based on the neurophysiological assessment, and quantitative gait analysis could also be considered as adjuncts approaches. These additional measurements/techniques are not widely incorporated as stand-alone due to device cost, operational complexity, and lack of defined relationships to current outcome measures.[2,7] The place of all of these options in the measurement ecosystem is not well defined and what is appropriate for routine care or clinical trials remains elusive.

The measurement of important features of disease impact remains discordant with clinicians focusing on the visible physical symptoms while patients live with the multifactorial impact including both the visible physical disability and the invisible impact (cognition, social isolation, etc.).[10] Hence, a shared approach including both patient and clinician perspectives on disease impact and treatment response could be highly advantageous to improve insight into spasticity impact. Considering the advances in pharmacological and rehabilitative treatments, improved development of reliable and valid measurements of spasticity should not be delayed by the ease and 'popularity' of the MAS. The need for a holistic path to address this unmet need for an enhanced multidimensional reliable validated approach to assess spasticity impact and treatment response for PwMS is urgent.

Declarations

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Not applicable.

Consent for publication

No patient data were used in this manuscript.

Author contributions

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