REVIEW

No Evidence of Disease Activity (NEDA) as a Clinical Assessment Tool for Multiple Sclerosis: Clinician and Patient Perspectives [Narrative Review]

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ABSTRACT

The emergence of high-efficacy therapies for multiple sclerosis (MS), which target inflammation more effectively than traditional disease-modifying therapies, has led to a shift in MS management towards achieving the outcome assessment known as no evidence of disease activity (NEDA). The most common NEDA definition, termed NEDA-3, is a composite of three related measures of disease activity: no clinical relapses, no disability progression, and no radiological activity. NEDA has been frequently used as a composite endpoint in clinical trials, but there is growing interest in its use as an assessment tool to help patients and healthcare professionals navigate treatment decisions in the clinic. Raising awareness about NEDA may therefore help patients and clinicians make more informed decisions around MS management and improve overall MS care. This review aims to explore the potential utility of NEDA as a clinical decision-making tool and treatment target by summarizing the literature on its current use in the context of the expanding treatment landscape. We identify current challenges to the use of NEDA in clinical practice and detail the proposed amendments, such as the inclusion of alternative outcomes and biomarkers, to broaden the clinical information captured by NEDA. These themes are further illustrated with the real-life perspectives and experiences of our two patient authors with MS. This review is intended to be an educational resource to support discussions between clinicians and patients on this evolving approach to MS-specialized care.

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PLAIN LANGUAGE SUMMARY

Recent progress in multiple sclerosis (MS) has led to the development of new treatments, known as high-efficacy therapies. Compared with previous treatments, high-efficacy therapies are better at managing visible inflammation of the central nervous system, a main cause of worsening symptoms early on in people living with MS. Treatment with high-efficacy therapies means many people with MS may achieve better outcomes than previously possible. One such outcome is the set of criteria known as no evidence of disease activity (NEDA). Achieving NEDA-3, the most commonly used NEDA criteria, means that people exhibit no clinical relapses, no worsening of physical symptoms, and no visible disease activity on a magnetic resonance imaging scan. Researchers have studied NEDA as an outcome in MS clinical trials, but it may be useful in clinical practice as a tool for doctors to measure a person's disease progression and response to treatment. This could help to inform important decisions around treatment selection and improve overall care for people with MS. This review explores the available information about NEDA to understand its potential to support clinical decision-making and patient evaluations. We discuss the barriers to NEDA being used in clinical practice and the ways the criteria may change to capture a broader range of clinical information from the patient. These topics are presented alongside the real-life perspectives and experiences of our two patient authors with MS. This review is meant to be an educational resource to assist conversations about NEDA between clinicians and patients in everyday clinical practice.

Keywords: Clinical practice; High-efficacy therapies; Magnetic resonance imaging (MRI); Multiple sclerosis; NEDA-3; No evidence of disease activity; Patient perspectives

Key Summary Points
No evidence of disease activity (NEDA) is a composite outcome measure used to assess response to treatment in multiple sclerosis and has primarily been used as an endpoint in clinical trials.
There is growing interest in the use of NEDA as an assessment tool to help patients and clinicians navigate treatment decisions in the clinic, particularly with the increasing availability of disease-modifying therapies (DMTs) that can more effectively mitigate inflammatory disease activity than traditional DMTs.
This review summarizes the current use of NEDA in clinical and real-world settings and its relevance to evolving treatment paradigms in the field of MS care, with the aim of facilitating shared decision-making in clinical practice.
We identify the current challenges to the implementation of NEDA in clinical practice and discuss the proposed methods to broaden the scope of NEDA to include other important parameters, such as neurodegeneration, that might be beneficial to improving clinical care for patients with MS.
The discussion is supplemented by first-hand perspectives and experiences of our two patient authors with MS, who provide some real-world context on NEDA and MS management in clinical practice.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune neurological condition that affects the central nervous system (CNS) and may lead to progressive and permanent disability [1]. The most common subtype of MS is relapsing–remitting MS (RRMS), which initially affects approximately

85% of patients diagnosed with MS and is characterized by acute neurological attacks (relapses) that may be followed by complete or partial recovery [2]. Some people with RRMS may eventually transition to secondary progressive MS (SPMS), in which there is ongoing decline of neurological function and accumulation of disability that is independent of relapses [1]. A minority (10–15%) of patients are affected by primary progressive MS (PPMS), a form that is progressive from disease onset [2].

The primary goals of current MS disease-modifying therapies (DMTs) include prevention or reduction of relapses and focal inflammatory lesions, along with mitigating disease progression and neurodegeneration [3]. DMTs for MS have been available in the USA since 1993 and are most impactful against the early inflammatory aspect of MS, exhibiting immunomodulatory and/or immunosuppressive effects [4, 5].

High-efficacy therapies (HETs; natalizumab, alemtuzumab, cladribine, ocrelizumab, ofatumumab, ublituximab, rituximab used off-label), which may be classified differently depending on the study, are distinct from low- and moderate-efficacy DMTs (glatiramer acetate, interferon beta, teriflunomide, dimethyl fumarate, sphingosine-1-phosphate receptor modulators) because they seem to impact inflammation more robustly [6–8]. This has led to a shift in disease management toward achieving the outcome assessment known as no evidence of disease activity (NEDA) [9, 10].

NEDA is a composite assessment based on both clinical and radiological criteria to evaluate the treatment efficacy of DMTs in patients with MS [11]. The most common NEDA definition, NEDA-3, is a composite of three related measures, namely no clinical relapses, no sustained disability progression (as defined by no increase in Expanded Disability Status Scale [EDSS] score), and no activity seen on magnetic resonance imaging (MRI; new or enlarging T2 hyperintense lesions or gadolinium-enhancing lesions) during a specified time period, usually 3–12 months [10].

The concept of NEDA has been explored predominantly in clinical trials, but there is growing interest in its use as a tool to help patients and healthcare professionals (HCPs)

navigate treatment decisions in the clinic. Certain therapies, such as HETs, can help patients achieve NEDA as a clinical outcome. Hesitancy about adopting NEDA as a treatment target in MS care is largely due to unfamiliarity with or disagreement about how to implement NEDA in clinical practice. Raising awareness about NEDA, as is the intention of this review, may therefore empower patients and clinicians to introduce NEDA as an aim in clinical practice as part of a shared decision-making approach to MS management. Such an approach could meaningfully improve outcomes and quality of life for patients.

To this end, this article draws on evidence from clinical practice and the perspectives and experience of our two patient authors, Seth Morgan, MD, and Cherie Binns, RN, MSCN. Seth Morgan is a retired board-certified clinical neurologist and ongoing vocal advocate for patients with MS who was diagnosed with MS in 2004. Cherie Binns is a certified MS nurse and Patient Healthcare Liaison for the Multiple Sclerosis Foundation who was diagnosed with MS in 1994.

This review intends to address the knowledge gap among neurologists, clinicians, and patients who may have encountered NEDA as a concept but are unsure how it applies to clinical practice. We discuss the current use of NEDA, the present challenges to its use in clinical practice, and the potential amendments to optimize the NEDA composite. By placing this information in the context of the changing treatment landscape, we intend for this article to function as a resource to facilitate discussions between clinicians and patients on this evolving approach to MS-specialized care.

METHODS

This article provides qualitative insights from HCP and patient authors, all of whom are from the USA and have a background in MS care, placed in the context of currently available literature. All authors liaised to select key data to include in the manuscript. Insights from the patient perspective as provided by Cherie Binns and Seth Morgan (henceforth referred to as patient authors) were collected via email in

response to a formal set of questions drafted by a Novartis employee and from general author discussions and email correspondence. As these insights were specific to the patient authors' personal experiences, generalizability to the wider MS community may be limited. Where possible, the patient authors' perspectives have been supported by published articles and patient surveys to minimize bias.

Published references and online resources relating to MS and NEDA were identified through PubMed literature searches of articles primarily published in the last several years, using search terms such as "multiple sclerosis[title/abstract] AND no evidence of disease activity[any field]" and appending search terms depending on the topic, such as "AND brain volume loss[title/abstract]".

Compliance with Ethics Guidelines

This article does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT USE OF NEDA

Origin and Rationale

MRI has historically been an important tool for visualizing lesion-based inflammation and evaluating treatment effects in MS. However, the radiographic absence of new or enlarging lesions on MRI does not necessarily correlate with disease inactivity [12]. Moreover, the prognostic value of relapses and inflammatory activity on MRI is inconsistent among patients who are receiving DMTs or not, which has led to increasing uncertainty on the full impact of such metrics (independently) on future disability [13]. These observations generated interest in NEDA as a treatment target for patients with MS. The purpose of NEDA is to provide a more comprehensive assessment of treatment effects and disease status than each clinical or MRI parameter can accomplish individually [10, 12].

NEDA-3 is derived from the post hoc analyses of contemporary phase 3 clinical trials in patients with MS, initially appearing in the AFFIRM trial (NCT00027300) for natalizumab [14] (Table 1).

NEDA-3 is not widely used as a primary outcome in clinical trials because MRI activity is not accepted as a surrogate marker of CNS inflammatory activity by regulators [10]. Since AFFIRM, multiple studies have included NEDA-3 generally as a secondary, exploratory, or post hoc endpoint. These include CLARITY (NCT00213135) for cladribine, OPERA I/II (NCT01247324, NCT01412333) for ocrelizumab, and ASCLEPIOS I/II (NCT02792218, NCT02792231) for ofatumumab, among others [15, 16, 19].

Clinical Trial Data and Real-World Evidence

Data from clinical trials have highlighted the potential of targeting NEDA in patients with MS to evaluate treatment effectiveness and response. As a general observation from these clinical trials, NEDA-3 status at 1–2 years on treatment was achieved by significantly more patients receiving a DMT versus placebo [14, 24, 26, 30, 31].

NEDA-3 has been successfully evaluated in several real-world settings [32–38]. A systematic review and meta-analysis of observational and clinical trial extension studies found NEDA-3 is associated with no long-term disability progression in RRMS [39]. Similarly, the real-world CLIMB study, which included clinical evaluation every 6 months and yearly MRIs for 219 patients with clinically isolated syndrome or RRMS, found that NEDA-3 status at 2 years is optimal for predicting long-term disability [40]. However, direct comparisons of the proportion of patients achieving NEDA-3 across real-world studies are hindered by inherent differences in study design, cohort demographics, and DMT history.

Furthermore, there is a lack of alignment among NEDA definitions and methodologies across clinical trials and real-world studies. EDSS thresholds for confirming disease progression differed between studies [14, 24, 38], as did the time frames for defining disease progression (12 weeks, 3 months, or 6 months) [24, 30, 33, 36, 41]. Studies also varied on the inclusion of

Table 1 NEDA-3 and NEDA-4 as endpoints in clinical trials

Clinical trial	Drug	Patient population	NEDA-3 as endpoint	NEDA-4 as endpoint
CLARITY [15]	Cladribine	RRMS	Post hoc	–
OPERA I/II [16]	Ocrelizumab	RMS	Secondary	–
CASTING [17]	Ocrelizumab	RRMS	Primary	–
CHORDS [18]	Ocrelizumab	RRMS	Primary	–
ASCLEPIOS I/II [19, 20]	Ofatumumab	RMS	Exploratory	Secondary
OPTIMUM [21]	Ponesimod	RMS	Exploratory	Exploratory
ULTIMATE I/II [7]	Ublituximab	RMS	Secondary	–
DEFINE/CONFIRM [22]	Dimethyl fumarate	RRMS	Post hoc	–
AFFIRM [14]	Natalizumab	RRMS	Post hoc	–
STRIVE [23]	Natalizumab	RRMS	Primary	–
FREEDOMS [24]	Fingolimod	RRMS	Exploratory	Post hoc
PANGAEA 2.0 [25]	Fingolimod	RRMS	–	
ADVANCE/ATTAIN [26, 27]	Peginterferon-β1a	RRMS	Post hoc	–
PRISMS [28]	Interferon-β1a	RRMS	Exploratory	–
EVIDENCE [29]	Interferon-β1a	RRMS	Post hoc	–

NEDA no evidence of disease activity, *NEDA-3* 3-parameter no evidence of disease activity, *NEDA-4* 4-parameter no evidence of disease activity, *RMS* relapsing multiple sclerosis, *RRMS* relapsing–remitting multiple sclerosis

both new and enlarging T2 hyperintense lesions or only new T2 hyperintense lesions [14, 36–38], and the inclusion of gadolinium-enhancing lesions [14, 24] in MRI assessments. The time period over which NEDA-3 was assessed also changed according to each study design, ranging from 24 weeks to 10 years [26, 35]. Although the removal of enlarging T2 hyperintense lesions was based on poor inter-rater agreement in routine clinical practice [36], the lack of standardization in component measures and time frames may make NEDA difficult for HCPs and patients to understand and to implement in clinical practice.

One observational retrospective study sought to address the inconsistent reporting of NEDA data by demonstrating the feasibility of using a systematic and consistent methodology to assess NEDA in the clinic [42]. Clinical and MRI data from 590 patients receiving fingolimod were collected from 33 MS centers and systematically analyzed to determine the proportion of patients achieving NEDA-3 (58.7%) in clinical practice over a median follow-up period of 16 months [42].

The BARTS-MS TREAT-2-TARGET-NEDA algorithm proposed by MS specialists shows a method of implementing NEDA-3 as a principal aim in managing relapsing MS in clinical practice [10]. This approach advises switching between DMTs or re-dosing induction therapy in cases of suboptimal response or breakthrough disease that occur following a re-baseline period. Re-baselining is recommended to assess disease status after initiation of a DMT at a point where patients are not experiencing breakthrough disease activity, to best observe treatment effect over time [11]. The re-baseline

Table 2 Patient authors' experiences of NEDA and MS management in the clinic

NEDA	Patient perspectives
Value	"Newly diagnosed patients… often seem to find a 'ray of hope' when NEDA is mentioned and explained and… it lends empowerment to them staying the course with a treatment regimen"
	"Those of us who have stabilized and are living with NEDA are just plain grateful"
	"I find that often [older/experienced patients] have… become resigned to disease progression and may have chosen to forgo further use of DMTs due to side effects or reluctance of a non-MS provider to be assertive in guiding them through the decision-making process"
Perception	NEDA has been brought up and discussed [in social media support groups for PLwMS] on several occasions…. Individuals have expressed the idea that NEDA is as close to a cure as they will likely see during their lifetime"
	"[The patient perception of NEDA is] confusion. Those told that their MRI shows 'no evidence of disease activity' cannot understand the disconnect between the test result and the clinical status"
	"The problem [confusion about NEDA] is potentially aggravated if their medical provider is not an MS specialty neurologist (such as a general neurologist or… a primary care physician)"
Barriers	"Cost is huge! Many individuals are underinsured and cannot afford the copays…. These individuals often rely on Medicare as their health insurance and all of the self-administered DMTs have HUGE copays of $2000–3000 each month"
	"The foundations that help with copays may say the individual has been approved for a year of copay assistance when… it may be 2 or 3 months before the Medicare payout year resets and they are dropped again. Drug companies have not found a way to support these patients"
	"Potential for payer denial and coverage…. Use of NEDA as a reason for treatment denial is a potential, real concern"
	"Misuse of NEDA being interpreted as being equivalent to 'a cure' by insurers may delay needed ongoing intervention to forestall or prevent disease progression"
Optimization	"The primary focus/starting point should not be the MRI status but the clinical patient symptoms with MRI results (if they are needed at all) being based on patient symptoms and clinical evaluation"
	"We need to address common sense things like hydration, sleep hygiene, elimination of distractions, diet, and exercise before moving on to costly testing"

DMT disease-modifying therapy, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *NEDA* no evidence of disease activity, *PLwMS* people living with multiple sclerosis

period depends on the pharmacodynamics of the DMT and is usually 3–6 months after treatment initiation but can exceed 12 months for slower-acting DMTs, such as alemtuzumab [11, 43].

Despite these efforts to demonstrate the practicability of targeting NEDA-3 in a clinical setting, an important caveat is that patients can lose NEDA status over time. For instance, the CLIMB study reported a steady loss of NEDA-3 status over the 7-year follow-up period [40]. Results from the study also reported that up to 43% of patients lost NEDA-3 status according to either clinical or MRI criteria, but not both, showing a dissociation between radiological and clinical disease activity [40]. Disability accrual in MS occurs mainly due to incomplete recovery from relapses (i.e., relapse-associated worsening [RAW]) and gradual clinical progression from the onset of disease (i.e.,

progression independent of relapse activity [PIRA]) [44]. Emerging evidence suggests PIRA may be the most important contributor of disability progression, more so than RAW and the presence of new focal inflammatory lesions [44–46]. PIRA has also been called silent progression to encompass the long-term worsening associated with accelerated brain atrophy in patients with relapsing MS, which is largely independent of relapse activity [47]. Silent progression, which has been characterized more effectively in recent years [47], has implications for the reliability of NEDA-3, especially as PIRA can occur in patients who also fulfill NEDA-3 criteria [48]. This is discussed further in the "Challenges for NEDA in Clinical Practice" section.

Patient Perspective on NEDA in Clinical Practice

Insights provided by our authors with MS (Table 2) indicate that the concept of NEDA can provide encouragement to (usually newly diagnosed) patients who feel motivated to maintain treatment adherence to achieve NEDA. In this sense, NEDA is often considered by patients to approximate a "cure". Some commentators share this opinion and have proposed one definition of an MS cure to be cumulative NEDA-3 for at least 15 years after initiating treatment [49].

It is therefore important to communicate to patients that NEDA can miss vital information that could identify ongoing disease activity or progression [50]. Indeed, some patients may be confused about the disconnect between an MRI test result showing "no radiographic evidence of disease activity" and their experience of having new, progressive, or persistent symptoms. Their experience of ongoing disability progression can continue even after commencing DMT, due in part to previous damage and advancing age [44].

Patients with more advanced MS may be less likely to discuss or target NEDA in the clinic as a result of their experience of stabilized or worsening disability, ineffective treatment options, or insufficient support from their clinician or neurologist in guiding their treatment decisions. The last of these may be amplified if their medical provider is not an MS specialist neurologist, such as a general neurologist in rural areas where neurology specialists are not readily available. Moreover, inequalities in and barriers to accessing healthcare services for adults with MS include, but are not limited to, demographic, socioeconomic, and geographic factors, and lack of patient education and support [51, 52].

Although the perceived value of NEDA varies among patients, discussion and comprehension of MRI results appear to be more well established in the clinic. Both patient authors report having frequent discussions about MRI results with their MS specialist neurologist or neuroradiologist. They agree that MRI results must be considered in tandem with the broader clinical picture to encompass patient symptoms and neurologic exam changes, which are important elements that contribute to a clearer understanding of the overall disease activity status. From a technological standpoint, relying on traditional, standard-of-care MRIs to assess clinical status would only capture macroscopic but not microscopic disease activity, a potentially critical oversight.

Per a shared decision with their HCPs, both patient authors only undergo MRI testing when they specifically request it and/or when experiencing worsening of symptoms. This aligns with consensus guidelines on the use of MRI in MS, which recommend evaluation with MRI after each unexpected clinical presentation (e.g., disease activity, suspected comorbidities, or adverse effects of treatments) and less frequent routine scans depending on the patient's duration and stability of disease [53]. MS clinicians largely rely on MRI monitoring in their treatment decisions, according to findings from the MSBase patient registry [54]. There does appear to be a shift occurring toward targeting NEDA-3 as clinicians use low lesion thresholds as the basis for switching DMTs, although the ubiquity of this approach depends on the availability of sensitive MRI technology and neurology clinicians [43, 54].

CHALLENGES FOR NEDA IN CLINICAL PRACTICE

Even with the availability of treatment algorithms and real-world data, the absence of

systematic methodology and standardized measurement recommendations or definitions represents a barrier to implementing NEDA in clinical practice [10, 11, 32].

Composite assessments such as NEDA may have improved sensitivity for detecting disease activity but are still beholden to the limitations of their individual parameters [12]. In clinical practice, these individual components may be impractical or inaccessible [55]. For instance, the regular MRI testing essential for targeting NEDA depends upon availability of specialist neurologists and technology, financial resources, and the healthcare system [56]. Brain MRIs provide valuable information, but there is a recognized need for spinal cord imaging in many patients to better inform neurological status over time [43, 57]. Consensus guidelines advise on which core sequences are important at baseline and for monitoring disease status over time [43]. Achieving NEDA may only be possible within a short therapeutic window early in the disease course [56]. According to natural history studies, MS is characterized by an early inflammatory phase leading to mild, or in some cases severe, physical disability [58, 59]. Neurodegeneration and cognitive decline also occur from the outset of MS and progressively worsen over time, but this may not be apparent until brain function decline has reached a certain threshold [60]. An early intervention strategy to limit early inflammation may therefore maximize the chance of achieving NEDA and mitigate neuronal damage, thus prolonging the physical independence of the patient. The observation that relapse rate in the early stage of disease is correlated with future disability, whereas later relapses are not, further supports this strategy [61].

While NEDA-3 status has been associated with long-term disability outcomes, its utility as a prognostic tool is limited [62]. This is to be expected because NEDA is a binary composite measure derived from granular neurological information that can only be maximally as prognostic as its individual components. Clinicians should remain cognizant in their communications with patients that while NEDA-3 is a valuable treatment goal, it cannot predict future disease severity.

The absence of any evidence of disease activity as measured by NEDA should not be taken as evidence that there is no disease activity taking place. There are concerns that NEDA-3 may not be able to capture subtle changes of inflammation and neurodegeneration that underlie disability [55]. Cases of prognostic misclassification can occur, where patients experience RAW or PIRA despite previously achieving NEDA-3 status [48, 62, 63]. PIRA may continue to contribute to disability progression in patients irrespective of their NEDA-3 status or MRI activity [47, 62, 63], which may explain why NEDA-3 is not always maintained long term [40, 48].

In clinically stable patients with NEDA-3, PIRA occurs even in the absence of MRI activity and has been associated with prognostic risk factors such as older age at treatment initiation and presence of MS-related spinal cord lesions [48, 63]. From this perspective, NEDA-3 and PIRA appear to reflect different aspects of disease progression, with NEDA-3 focusing on the inflammatory component and PIRA capturing the "silent progression" and neurodegenerative components of the disease. As such, NEDA-3 can be considered a clinical tool for assessing observable features of disease activity, whereas PIRA describes progression separate from NEDA-3. Therefore, it may be suggested that clinicians not only utilize NEDA as a target outcome measure but do so alongside assessments of PIRA to more fully appreciate the scope of disease. Studies have defined PIRA as 3 or 6 months of confirmed disability worsening (measured by EDSS score) in the absence of relapses [44] or using a composite of EDSS score combined with hand coordination (9-Hole Peg Test [9-HPT]) and walking ability (Timed 25-Foot Walk [T25-FW]) [46].

Finally, there is debate around whether NEDA-3, being weighted toward inflammatory disease processes, is a suitable measurement for PPMS, a subtype of MS characterized by progressive disability and minimal inflammatory activity on MRI [2]. Most MS medications are indicated for relapsing MS and, accordingly, NEDA-3 may have the most applicability as a treatment target in patients with this subtype. One real-world study reported similar

proportions of patients achieving NEDA-3 with RRMS (62.1%), PPMS (54.6%), and SPMS (55.1%) after 2 years on ocrelizumab, with no apparent distinction between assessment criteria for PPMS and relapsing MS [64]. Others have defined NEDA in a population of patients with PPMS to omit the relapse component and only include absence of EDSS progression and no new MRI lesions [65]. The latter might represent the most realistic approach to target NEDA in a real-world setting for patients with PPMS until more advanced techniques for tracking disease progression reach the clinic. Otherwise, PIRA or a combination of PIRA and NEDA might better capture the non-relapse-associated and largely MRI activity-independent progression associated with PPMS and non-active SPMS.

The complex nature of MS pathophysiology and the technological and practical challenges to implementing NEDA-3 in clinical practice represent barriers to its widespread use, but with some adaptation to a real-world setting, these barriers may not be insuperable.

OPTIMIZATION OF NEDA AND ALTERNATIVE OUTCOMES OF DISEASE

Alternatives or amendments to NEDA-3 aim to address concerns that the assessment may not adequately capture all aspects of a patient's clinical status because of a high degree of disease heterogeneity [11]. Options for adapting NEDA to a clinical setting are summarized in Table 3.

NEDA-4 with Brain Volume Loss

Because NEDA-3 has a strong focus on the inflammatory components of MS, brain volume loss (BVL), as determined by MRI, has been proposed as a fourth component to NEDA (NEDA-4) to capture the neurodegenerative components [10, 11, 24]. Proportionally more patients achieve NEDA-3 (approx. 58%) than NEDA-4 (29–37%), suggesting that addition of BVL increases the stringency of the assessment

[42, 55], thereby potentially mitigating prognostic misclassification.

BVL occurs at a yearly rate of 0.5–1.35% in patients with MS versus 0.1–0.3% in healthy controls [79], and is predictive of physical disability [80, 81], cognitive function [82], and progression to SPMS [55]. At present, while NEDA-4 with BVL has been well defined in the literature for clinical studies, BVL cannot be routinely measured in clinical practice because of technological limitations and concerns that longitudinal brain volume assessment is unreliable, due in part to confounding physiological factors [43].

Potential Additional Components to the NEDA Composite

Novel MRI measures can capture additional information. Cortical gray matter lesions contribute to disease progression and could be used as a marker of individual disease progression in clinical practice [43]. Chronic active lesions, such as slowly expanding lesions, reflect ongoing tissue damage and could be considered MRI markers of chronic inflammatory activity [43]. However, as with BVL measurements, routine MRI has poor sensitivity for advanced imaging protocols and requires standardized image acquisition and analysis before implementation in clinical practice [43, 83].

Because the practicability of longitudinal BVL in routine clinical care is limited, other proposed NEDA components assess neurodegeneration using more accessible methods. Acquiring different retinal measures by optical coherence tomography (OCT) is considered a non-invasive way to assess neurodegeneration in the cerebral structures of patients with MS [84]. OCT measures of retinal thickness are associated with brain atrophy and cognitive deficits [84–86], and have been proposed as a predictor of early cognitive impairment in MS [84, 87]. Moreover, baseline retinal measures appear to be associated with long-term disability [88].

Cognitive impairment negatively impacts patients' daily functioning and quality of life [89]. Cognitive deterioration has been shown to

Table 3 Clinical assessments used to evaluate MS

Assessment	Description	Considerations
EDSS [56, 66, 67]	Assessment of disability in 7 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, cerebral) and ambulation	• Widely used in MS clinical trials • Limited sensitivity in the lower ranges and with subtle changes • Fatigue and cognitive function are not adequately measured • Variable intra- and inter-rater reliability
EDSS-Plus [68]	Composite assessment of 3 physical disability parameters to facilitate evaluation of disability progression: 1. EDSS 2. T25-FW 3. 9-HPT	• More sensitive than the EDSS in identifying disability progression • Suitable measure for SPMS and PPMS, but the EDSS alone is better for RRMS • May be difficult to distinguish between RRMS and early SPMS in real-world clinical practice
NEDA-3 [11, 69]	Composite assessment of 3 parameters, weighted toward neuroinflammation: 1. No disability progression based on EDSS score* 2. No Gd+ lesions and no new/enlarging T2 hyperintense lesions on MRI 3. No clinical relapses	• Focus on inflammatory components of disease • Complements use of HETs but may expose patients to safety risks • Predictive of long-term disability if targeted early • Limited sensitivity with subtle changes • Does not capture full scope of clinical information
NEDA-4 [24]	Composite assessment of 4 parameters, includes neuroinflammation and neurodegeneration: 1. No disability progression based on EDSS score* 2. No Gd+ lesions and no new/enlarging T2 hyperintense lesions on MRI 3. No clinical relapses 4. Brain volume loss < 0.4% on MRI	• Addition of brain volume loss as a surrogate for disability and cognitive function • Currently not routinely measured in MS MRI sequences
MSFC	Quantitative measure of physical and cognitive function: 1. Leg function and ambulation (T25-FW) 2. Hand/arm function (9-HPT) 3. Cognitive function (PASAT)	• Considered more sensitive with the same patient over time • Practicable for everyday clinical use • Correlates with quality of life metric • The PASAT is difficult to administer
SDMT [70]	Assessment of cognitive function	• Better predictive validity and easier to administer than the PASAT

Table 3 continued

Assessment	Description	Considerations
MSDM [56]	Alternative criteria for assessment of NEDA to support early treatment adjustment: 1. Disability progression (modified MSFC: T25-FW, 9-HPT, addition of LCSLC, SDMT instead of PASAT) 2. Number, severity, and type of relapses 3. MRI findings (Gd+ lesions, new/enlarged T2 lesions) 4. Neuropsychology: fatigue (FSMC), depression (HADS), anxiety (HADS), quality of life (MSIS-29)	• Practicable for everyday clinical use • Can detect clinical changes even in early stages of disease • Good sensitivity • Neuropsychology domain considered increasingly important
MEDA		
MEDA (MAGNIMS score) [71]	Based on the MAGNIMS "low" risk score for future disability, defined as: 1. No relapses 2. ≤ 2 contrast-enhancing lesions	• Good accuracy in predicting severe long-term disability • May be more realistic for some patients to achieve in clinical practice • Low positive predictive value • Not verified in patients treated with oral DMTs or HETs
Rio score [72] [73]	Scoring system (range 0–3) to identify patients with poor short-term responses to therapy in the first year on treatment: 1. MRI findings (1 point if > 2 active T2 lesions) 2. Number of relapses (1 point if ≥ 1 relapse) 3. Disability progression (1 point if EDSS score increased by ≥ 1 point for ≥ 6 months)	• Can identify patients at risk of having a poor response to treatment • Disability progression in first year of treatment may be a poor predictor of subsequent clinical activity
Modified Rio score [69, 73]	Simplified version of the Rio score (range 0–3) that omits disability progression: 1. MRI findings (1 point if > 5 new T2 lesions) 2. Number of relapses (1 point if 1 relapse; 2 points if ≥ 2 relapses)	• Uses long-term data to improve upon the Rio score • Predictive value in different ethnic cohorts and for other DMTs • Difficulty classifying patients with an intermediate score

Table 3 continued

Assessment	Description	Considerations
PROs [74–78]	Incorporates patients' experience of non-clinical or invisible symptoms into assessment of disease status: • Quality of life (SF-36, MSQOL-54, MSQLI, MSIS-29) • Multidomain: physical, cognitive, quality of life (Neuro-QoL)	• Can be completed before the appointment at home or while waiting in the office

9-HPT 9-Hole Peg Test, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *FSMC* Fatigue Scale for Motor and Cognitive Functions, *Gd+* gadolinium-enhancing, *HADS* Hospital Anxiety and Depression Scale, *HET* high-efficacy therapy, *LCSLC* low-contrast Sloan letter chart, *MAGNIMS* magnetic resonance imaging in MS, *MEDA* minimal evidence of disease activity, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MSDM* multiple sclerosis decision model, *MSFC* Multiple Sclerosis Functional Composite, *MSIS-29* Multiple Sclerosis Impact Scale, *MSQLI* Multiple Sclerosis Quality of Life Inventory, *MSQOL-54* Multiple Sclerosis Quality of Life-54, *NEDA* no evidence of disease activity, *NEDA-3* 3-parameter no evidence of disease activity, *NEDA-4* 4-parameter no evidence of disease activity, *PASAT* Paced Auditory Serial Addition Test, *PPMS* primary progressive multiple sclerosis, *PRO* patient-reported outcome, *RRMS* relapsing–remitting multiple sclerosis, *SDMT* Symbol Digit Modalities Test, *SF-36* 36-Item Short Form Survey, *SPMS* secondary progressive multiple sclerosis, *T25-FW* Timed 25-Foot Walk

*Differences exist in definitions of EDSS-based worsening disability between studies [11]: one proposed definition of worsening disability is an increase in EDSS score of 1.5 points from baseline score of 0, an increase of 1.0 points from baseline score of ≥ 1.0, or an increase of 1.5 points from baseline score of ≥ 5.0, confirmed after 3 or 6 months [24]

occur in patients that met NEDA criteria [90]. As such, it has been proposed that a validated cognitive assessment, the Symbol Digit Modalities Test (SDMT), be incorporated into NEDA-4 in place of BVL as a way to provide information on the neurodegenerative aspects of MS [91], although a recent study demonstrated that changes in SDMT did not accurately reflect decline in cognition over time [92].

The multiple sclerosis decision model (MSDM) is a 4-domain model based on NEDA-3 that retains the relapse and MRI lesion components (Table 3) [56] but uses a modified version of the Multiple Sclerosis Functional Composite (MSFC) score in place of the EDSS [93, 94]. The MSFC score correlates with disability status and brain atrophy [56, 95] and has components that are easily teachable to clinical staff [93, 94]. The fourth domain of the MSDM is neuropsychology that covers factors increasingly important to patients and neurologists, such as fatigue, anxiety, depression, and quality of life. This adaptation of NEDA-3 aims to aid early treatment decisions and treatment failure in clinical practice [56]. Importantly, composite scores based on the EDSS and domains of the MSDM and MSFC (SDMT, Paced Auditory Serial Addition Test, 9-HPT, T25-FW) may also be used to define PIRA events with high sensitivity [46–48].

Patient-reported outcomes (PROs) collected using standardized questionnaires can provide value to these scoring systems as well as insight into the patient's perspective of treatment success, which may differ from the clinician's perspective based on clinical measures [96]. PROs may be useful for raising concerns about invisible symptoms, which may be stigmatized or not commonly addressed in HCP–patient conversations [97]. As a potential complement to PROs and standardized outcomes, motion sensors embedded in smartphones and wearable devices can be used to monitor everyday physical ability, fatigue, exercise, and quality of sleep in patients with MS, thus providing more contextual information for clinical decision-making [98].

Some assessments are less stringent than NEDA-3, such as the Rio score [72] and the modified Rio score [73], which allow for

minimal evidence of disease activity (MEDA) defined as no relapses and no more than two new focal T2 lesions in the absence of contrast-enhancing lesions [71]. This approach is based on concerns that HETs may preemptively expose patients to greater safety risks and should be avoided in favor of moderate-efficacy DMTs [10]. Supporters of targeting MEDA claim it is better suited for early treatment optimization and may represent a more realistic goal in clinical practice [99, 100]. It could be considered questionable to permit breakthrough disease activity, given that focal inflammatory lesions and early-stage relapses are associated with a poorer long-term prognosis [61, 101].

Biomarkers as Components of NEDA

Ongoing clinical trials are prospectively evaluating clinical and paraclinical biomarkers of MS for their potential to predict disability progression (Table 4). The addition of a biomarker component to NEDA may reveal underlying disease processes and PIRA, which could indicate disease trajectory, although NEDA would remain a disease activity measure and not a prognostic tool.

Neurofilament light chain (NfL) is a neuro-axonal protein found in cerebrospinal fluid (CSF) and released into the blood upon neuronal injury [106]. Blood NfL is a marker of MS relapses, lesion formation, axonal injury, and neuronal damage; it also correlates with treatment response and is associated with disease progression [106–114]. Plasma NfL can predict NEDA-3 status and has been proposed to replace the MRI component in NEDA-3 [115], or to be added as an extra component to NEDA-4, giving rise to 5-component NEDA (NEDA-5) [116, 117]. However, NfL use is currently limited by poor standardization of valid cutoff values, cases of borderline values, false negatives and false positives, and the confounding effect of comorbidities [115]. Serum NfL appears to correlate with CSF NfL but is variable and present at much lower levels than in the CSF [111]. As a routine clinical assessment, sampling serum NfL would be significantly more amenable to patients than a lumbar puncture but is hindered

by the need for longitudinal data regarding the kinetics of NfL following CNS lesions and the impact of aging along with comorbidities (e.g., obesity, diabetes, etc.). Regarding NEDA specifically, protocols need to be established to re-baseline for biomarkers in patients achieving NEDA to clarify the correlation between biomarkers, neurodegeneration, and NEDA without the confounding effect of relapses [116].

Glial fibrillary acidic protein (GFAP), an intermediate filament of astrocytes, is another emerging biomarker of CNS injury [118]. Studies have identified a correlation between blood GFAP levels and severity of disability, lesion burden, brain atrophy, and other markers of CNS injury such as NfL [118]. While GFAP could be a potential biomarker for disability progression [119, 120], the relationship between GFAP and NEDA status has not yet been evaluated.

Most of the approaches outlined here have potential but require validation before being used as a clinical assessment or decision-making tool. Addition of a neurodegeneration or cognitive function domain would be desirable to broaden the scope of NEDA assessment beyond the inflammatory component of MS. However, there is ongoing debate about the optimal components to include in the NEDA composite, with cognitive function metrics, biomarkers, patient outcomes, and others potentially giving rise to an 8-component NEDA [121], a metric that could be unrealistic for any one patient to achieve. Insights on the utility of these amendments will become clearer if research studies validate the various definitions and allow them to be adopted by more MS clinics in the future.

Patient Perspective on Alternative Outcomes and Biomarkers

There is a need for new disability outcome measures that better reflect the patient experience of MS than physical disability measures alone. Current outcome measures do not sensitively measure long-term change, patient-perceived health status, or quality of life [122].

Table 4 Summary of select MS clinical trials prospectively evaluating biomarkers

	DELIVER-MS [102, 103] (NCT03535298)	TREAT-MS [104] (NCT03500328)	MS-ReBS [105] (NCT05204459)
Description	RRMS Interventional, observational, prospective, R, PG, SB n = 800 (400 randomized and 400 observational-estimated) Follow-up 36 months	RRMS Interventional, prospective, R, PG, SB n = 900 (estimated) Follow-up 75 months	MS, MS-related conditions, and others Observational, prospective n = 1000 (estimated) Follow-up 10 years
Intervention	1. Early HET group 2. Escalation group	1. Early HET group 2. Traditional DMT group	N/A
Primary	• BVL from baseline	• Time to sustained disability progression using EDSS-Plus	• Identify risk factors for disability progression (peripheral blood biomarkers, retinal structure, visual function, longitudinal MRIs)
Secondary	• BVL from month 6 • Multidimensional composite assessing progression (EDSS, T25FW, 9HPT, SDMT, LCLA) • MSIS-29 • Neuro-QoL	• PDDS • SDMT • MSFC (original and include LCLA) • Relapse recovery • MSIS-29 • Neuro-QoL • Employment/marital status • Safety (SAEs, AEs leading to DMT switch or change in medication administration)	• Effect of DMTs on disability risk • Identify factors associated with visual disability and optic neuropathy in MS and related disorders • Identify serum, genetic, and stem cell-derived biomarkers influencing disability risks

Table 4 continued

	DELIVER-MS [102, 103](NCT03535298)	TREAT-MS [104](NCT03500328)	MS-ReBS [105](NCT05204459)
Tertiary/other	Biomarker discovery studies to evaluate predictors of longer-term disability and treatment response, with the goal to individualize treatment approaches in MS. Repository of biosamples collected includes frozen serum, whole plasma for DNA, and peripheral blood mononuclear cells	• Brain MRI (whole brain and normalized gray matter volumes, cortical thickness, subcortical gray matter compartment volumes, T2 lesion burden) • Number of relapses • New brain lesions on MRI • Retinal layer thicknesses by OCT • Number of new symptomatic interventions for MS-related symptoms • Biomarker discovery studies in parallel with DELIVER-MS	N/A

Presented data are correct as of July 30, 2023

9-HPT 9-Hole Peg Test, *AE* adverse event, *BVL* brain volume loss, *COVID-19* coronavirus disease 2019, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *HET* high-efficacy therapy, *LCLA* low-contrast letter acuity, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MSFC* Multiple Sclerosis Functional Composite, *MSIS-29* Multiple Sclerosis Impact Scale, *N/A* not applicable, *OCT* optical coherence tomography, *PDDS* Patient-Determined Disease Steps, *PG* parallel-group, *R* randomized, *RRMS* relapsing–remitting multiple sclerosis, *SAE* serious adverse event, *SB* single-blind, *SDMT* Symbol Digit Modalities Test, *T25-FW* Timed 25-Foot Walk

Our patient authors are generally cautious of biomarkers and their ability to have a substantive benefit in MS care, perceiving them as unreliable and secondary in importance to lifestyle factors such as diet, exercise, and sleep hygiene. While there is some interest in methods of assessing cognition, such as BVL monitoring and neuropsychiatric testing, such requests have been difficult or impossible to fulfill without the relevant infrastructure in place. In addition, while some PROs have been proposed as neuropsychological outcome measures in the MSDM [56], numerous PRO measures exist and consensus is needed on which are optimal in MS, especially over the longer-term disease course. Furthermore, each PRO measure comes with its own limitations that could restrict its application to NEDA.

There is concern from the patient authors that NEDA and its various iterations prioritize MRI status as a starting point, with clinical factors and patient symptoms as secondary considerations. Forgoing the patient experience of a disease to focus solely on clinical presentations can be viewed as counterintuitive to the spirit of patient-centered healthcare. A NEDA assessment that combines PROs of fatigue, anxiety, depression, and quality of life with physical and cognitive testing might be the best compromise to capture clinical and invisible symptoms, evaluate treatment effects, and better understand the experience of patients with MS. Alternatively, biomarkers might be of greater value to newly diagnosed patients whose clinical presentation has not yet been extensively characterized.

NEDA AND THE CHANGING TREATMENT LANDSCAPE

The ability of HETs to significantly suppress macroscopic MS disease activity has led to NEDA-3 being proposed as the principal aim for managing relapsing MS [10, 56]. There is a growing body of evidence that early initiation of HETs may have a more beneficial impact on long-term disease activity and progression and the best benefit/risk ratio compared with moderate-efficacy DMTs or delayed HET initiation [123–127]. HET treatment has been observed to significantly reduce neuroinflammatory activity as well as delay clinical disability, brain atrophy, and progression to SPMS [123–127]. Considering that cognitive decline starts early in the disease course and may be accompanied by a delayed clinical manifestation, initiating HETs as early as possible might be imperative, not only to target inflammation according to NEDA but also to contribute to reducing PIRA by mitigating or preventing subsequent neurodegeneration [60].

Current treatment guidelines tend to prioritize an "escalation therapy" approach focusing on lower-risk, moderate-efficacy DMTs, where patients have the option to switch to another similar therapy, and eventually to HET, if their treatment is not effective or well tolerated [128, 129]. HETs are then reserved early on for those with highly active MS, despite evidence that treatment initiation with HET increases a patient's chances of achieving NEDA. In the OPERA I/II trials, proportionally more patients receiving HET (ocrelizumab) for 96 weeks achieved NEDA-3 than with interferon-β1a [16]. Furthermore, a Norwegian real-world study found that achieving NEDA-3 in years 1 and 2 was significantly more likely in patients receiving HETs than moderate-efficacy DMTs, especially when used as a first-line therapy [130]. Patients switching to HET (ocrelizumab) as a result of suboptimal disease control in the phase 3b CASTING trial also experienced an overall higher NEDA-3 rate across numerous disease-related and demographic subgroups, regardless of previous treatment background [17]. Likewise, switching from teriflunomide to ofatumumab in the ALITHIOS open-label extension trial was associated with greater proportions of patients achieving NEDA-3, along with reduced lesion count, disability progression, and annualized relapse rate (ARR), albeit at lower rates than those who received early and continuous ofatumumab [131]. Neurodegeneration is substantially more likely to occur at similar rates to healthy controls in patients with MS who achieve NEDA-3 versus those who do not, according to a Belgian real-world study [132].

Findings from a large contemporary real-world study conducted by the MSBase Study Group also provide evidence of a strong protective effect of early DMT use against long-term disability worsening [133]. Early on-treatment relapse activity was also found to be an indicator of poor prognosis, suggesting patients may benefit from immediate escalation or HET initiation to mitigate RAW and achieve better long-term outcomes [133]. In general, confounding by indication is not accounted for by observational studies, nor is time to escalation consistently reported. Hence, the treatment effect between groups could be inflated and misleading. The TREAT-MS and DELIVER-MS trials' study designs will help prevent such limitations and data captured will be able to assess the impact of treatment strategies in a prospective, randomized, blinded fashion on NEDA-3 and beyond.

These clinical and real-world data lend support to the implementation of NEDA as a primary treatment goal in patients with relapsing MS to align with the rapidly changing landscape of MS therapies. Retrospective analyses of US administrative claims data have revealed some general treatment patterns from the past 10–20 years. Lower-efficacy DMTs, such as glatiramer acetate, interferons, and teriflunomide, continue to make up the majority (approx. 50%) of first-line treatments [134], whereas the proportion of patients initiating HET has been steadily rising in recent years to a current figure of around 40% [135, 136].

More than 80% of patients with MS have reported wanting an autonomous or shared role in the decision-making process [137, 138]. Shared decision-making between the patient and HCP is important to satisfy patient requirements and take advantage of available treatments. Switching among DMTs when breakthrough disease occurs appears to be a common practice, although this paradigm may change with evolving treatment options [139–141]. Patient perspectives from the NARCOMS registry revealed that the discussion to switch DMTs was initiated almost equally by physicians and patients [142], with physician recommendations regarding the specific therapy being the most frequently cited reason for switching DMTs, followed by perceived lack of efficacy. In addition, almost 85% of responders ranked the physician managing their MS as the most trusted source of treatment option information [142]. It is apparent that although patients desire an active role in their MS management, clinicians should aim to assume responsibility for introducing concepts such as NEDA, and meaningfully contributing to such discussions in the clinic.

Patient Perspective on DMTs/HETs

A patient's choice of MS therapy is often reflective of their individual preferences, lifestyle, and experience. When selecting an MS therapy, our patient authors consider efficacy, as defined by no relapses, disease stabilization, and noticeable control of progressive symptoms, to be the most important factor, followed by an absence of unacceptable side effects that might interfere with daily living.

Another important factor is the dosing schedule, which our patient authors acknowledge may not be a priority for all people with MS. In a formal survey, patients with MS considered infrequent dosing (e.g., twice yearly rather than once daily) to be an important aspect of their MS therapy in addition to route of administration, convenience, disease stabilization, and lack of adverse effects that impact well-being [143].

Achieving these criteria may involve switching medication, with the caveat that the inability of a DMT to improve pre-existing deficits or symptoms from MS should not be viewed as treatment failure. The currently available DMTs are used to prevent disease progression.

From the patient author perspective, one of the most significant barriers to accessing HET treatment and targeting NEDA is that of out-of-pocket costs. People with MS, especially those who are underinsured, can face unaffordable copays for the medication they have decided on with their healthcare team, sometimes exceeding thousands of dollars per month. Foundations and patient assistance programs exist to help with copay costs, but administrative

oversights can prevent patients from receiving the full year of coverage. Of considerable concern to our patient authors is the potential for payers to deny DMT coverage on the basis of a misinterpretation of NEDA as being equivalent to disease free (or a "cure"). In addition, if payers prioritize escalation therapy requirements on the basis of cost, they may not fully recognize the importance of maintaining a treatment course or strategy, which could prompt insurers to delay ongoing interventions necessary to mitigate disease progression.

These perspectives are supported by findings that a substantial proportion of patients rely on free/discounted drug programs, with rising drug costs and changing insurance coverage adversely affecting access to treatment for patients with MS [144]. Initiating and maintaining treatment can be influenced by several factors, including DMT licensing, prescribing guidelines, reimbursement, disease course, generics, and personal perceptions [145]. National/local policy makers and health insurance companies can decide which DMTs are covered by reimbursement, effectively dictating which DMTs are available to people with MS [145]. As an example, patients with PPMS or non-active SPMS (no recent relapses or new MRI activity) may have difficulty accessing treatment as a result of reimbursement restrictions [146].

RESOURCES FOR PATIENT EDUCATION

A large proportion of neurologists and advanced practice nurses have reported that they have little to no basic knowledge on neurological assessments such as NEDA [147], suggesting that HCP–patient discussions on NEDA may depend heavily on HCP awareness. MS specialist nurses often have a close relationship with people with MS, making them best suited to provide education, personalized care, and emotional support [148].

Online resources are the most accessible tools for patient education. Patient information sites such as My-MS.org and UK MS Trust explain NEDA in plain language (albeit with

some medical phrases) and discuss clinical study data on NEDA over time [149, 150]. The Multiple Sclerosis Association of America Ultimate MS Treatment Guide compares 19 different US Food and Drug Administration-approved MS treatments alongside first-hand experiences of medical experts and patient advocates so that people with MS can make an informed choice regarding available therapies [151]. Patients may also want to consider monitoring their symptoms using a tool such as Your MS Questionnaire [152] so they are more prepared to discuss treatment goals and NEDA with their HCP.

Ultimately, the best resources for patient education and guidance are MS providers. Exclusive use of online resources is not conducive to a personalized medicine approach in MS and may not produce the most relevant or targeted information for the disease characteristics of the individual patient [153].

This article aims to expand on the available information on NEDA in the public domain to increase familiarity with the concept and potentially encourage adoption in clinical practice. Professional societies may start to refer to reviews such as this one when optimizing treatment guidelines, which may ultimately improve care and outcomes for people with MS.

Patient Perspective

People with MS are increasingly benefiting from online resources to learn more about MS and its treatment options and emerging research and to connect with an online MS community [154–157]. A NARCOMS registry survey found that 60% of participants used the internet as their first choice for information about MS [158], similar to the State of MS survey, in which 72% of participants found online and social media resources to be most helpful for finding information about their condition [159].

According to one patient author, social media support groups are an important avenue for people with MS to discuss and understand treatment options. These groups provide opportunities for people with MS to seek real-

life views on the advantages and disadvantages of the medication suggested by their neurologist. As detailed in other patient perspectives, social media groups can empower patients to participate more fully in shared decision-making by improving their disease education, in addition to providing them with a sense of connection, purpose, and hope for the future [155, 156]. Of course, these groups may not be a suitable option for all people with MS.

Patients benefit when they are properly educated about their disease and treatment options [160] and when they have good relationships with their HCPs [161, 162]. Social media can facilitate health education, promote health behavior change, and improve access to health services [163, 164], but many patients are concerned about encountering potentially harmful misinformation on the internet [156]. There may be a need to provide patients and caregivers with tools for more discerning internet navigation that avoids biased search engine results, sponsored content, and incomplete or not up-to-date information [165]. Our patient authors source reliable information from recognized patient advocacy sites (e.g., National Multiple Sclerosis Society, Multiple Sclerosis Foundation, iConquerMS) or established medical centers and institutes (e.g., National Institutes of Health or other medical sites). Because HCPs are usually the most trusted source of health information [142], patients and HCPs should be encouraged to continue these discussions in the clinic.

Both patient authors have received extensive guidance from their HCPs on treatment decisions and managing their MS, including advice on interacting with insurance companies. It follows then that if NEDA is to gain traction as a clinical tool, a large portion of the responsibility rests with clinicians for not only leveraging these clinical discussions to demystify the concept for patients who might benefit but also remaining aware of the potential access barriers encountered by patients and advocating for solutions for them where possible.

CONCLUSION

To our knowledge, this is the first review to examine NEDA as a potential clinical tool from both the patient and clinician perspective. As therapeutic options for MS continue to expand, adopting treatment targets such as NEDA could present a more methodical approach to decision-making and could also help to develop a personalized approach to MS management that may ultimately benefit patient outcomes and monitoring.

Keeping HCPs, patients, and payers well informed on NEDA is imperative for it to be meaningfully integrated into everyday MS management and shared decision-making. For this to occur, there needs to be agreement within the medical field about the role for NEDA in clinical practice and concerted effort to conduct the research necessary to standardize its component definitions. All this must be performed with consideration of patient perspectives and experiences, so as not to inadvertently lose invaluable patient insights that may conflict with objective clinical data.

All authors of this article are or were HCPs with a background specializing in MS care. It is intended that the authors' insights and expertise will clarify some of the considerations for implementing NEDA in clinical practice and facilitate shared decision-making. The information herein could be strengthened by additional perspectives on NEDA from lay patients with MS and general (i.e., non-MS specialist) neurologists to help to identify the needs of and develop resources for those interested in targeting NEDA in MS.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Scott D. Newsome has received consulting fees for scientific advisory boards from Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, Horizon Therapeutics, Novartis, and TG Therapeutics; is an advisor for Autobahn; is the study lead principal investigator for a Roche clinical trial; and has received research funding (paid directly to institution) from Biogen, Department of Defense, Genentech, National Multiple Sclerosis Society, Patient-Centered Outcomes Institute, Roche, and Stiff Person Syndrome Research Foundation. Cherie Binns has received consulting fees from Novartis for manuscript development and advisory panels. Ulrike W. Kaunzner has participated in advisory boards for Genentech and Novartis. Seth Morgan has nothing to disclose. June Halper serves as a paid consultant to MS-LINK (an EMD Serono project); is a volunteer journal club speaker; and has received consulting fees from Novartis for manuscript development.

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