

Association of NEDA-4 With No Long-term Disability Progression in Multiple Sclerosis and Comparison With NEDA-3

A Systematic Review and Meta-analysis

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Abstract

Background and Objectives

No evidence of disease activity (NEDA)-4 has been suggested as a treatment target for disease-modifying therapy (DMT) in relapsing-remitting multiple sclerosis (RRMS). However, the ability of NEDA-4 to discriminate long-term outcomes in MS and how its performance compares with NEDA-3 remain uncertain. We conducted a systematic review and meta-analysis to evaluate (1) the association between NEDA-4 and no long-term disability progression in MS and (2) the comparative performance of NEDA-3 and NEDA-4 in predicting no long-term disability progression.

Methods

English-language abstracts and manuscripts were systematically searched in MEDLINE, Embase, and the Cochrane databases from January 2006 to November 2021 and reviewed independently by 2 investigators. We selected studies that assessed NEDA-4 at 1 or 2 years after DMT start and had at least 4 years of follow-up for determination of no confirmed disability progression. We conducted a meta-analysis using random-effects model to determine the pooled odds ratio (OR) for no disability progression with NEDA-4 vs EDA-4. For the comparative analysis, we selected studies that evaluated both NEDA-3 and NEDA-4 with at least 4 years of follow-up and examined the difference in the association of NEDA-3 and NEDA-4 with no disability progression.

Results

Five studies of 1,000 patients (3 interferon beta and 2 fingolimod) met inclusion criteria for both objectives. The median duration of follow-up was 6 years (interquartile range: 4–6 years). The prevalence of NEDA-4 ranged from 4.2% to 13.9% on interferon beta therapy and 24.9% to 25.1% on fingolimod therapy. The pooled OR for no long-term confirmed disability progression with NEDA-4 vs EDA-4 was 2.14 (95% confidence interval: 1.36–3.37; $I^2 = 0$). We did not observe any significant difference between NEDA-4 and NEDA-3 in the comparative analyses.

Discussion

In patients with RRMS, NEDA-4 at 1–2 years was associated with 2 times higher odds of no long-term disability progression, at 6 years compared with EDA-4, but offered no advantage over NEDA-3.

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Glossary

BVL = brain volume loss; **CI** = confidence interval; **DMT** = disease-modifying therapy; **EDA** = evidence of disease activity; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **NfL** = neurofilament light chain; **OR** = odds ratio; **PIRA** = progression independent of relapse activity; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting MS; **SPMS** = secondary progressive MS.

The use of composite outcome measures has become widespread in recent years as early targets for evaluating response to multiple sclerosis (MS) disease-modifying therapies (DMTs). No evidence of disease activity (NEDA) is one such measure. NEDA-3, the most commonly used iteration of NEDA, is defined as no evidence of (1) relapse, (2) disability progression, or (3) new or enlarging T2 and/or T1 gadolinium-enhancing lesion measured over the first 1–2 years on therapy.^{1,2} However, NEDA-3 has been criticized for being overly focused on inflammatory aspects of MS.³ Early⁴ and/or longitudinal⁵ brain volume loss (BVL) have been shown to independently predict long-term disability progression in relapsing-remitting MS (RRMS). Subsequently, NEDA-4 was introduced to include no significant annual BVL in addition to the NEDA-3 criteria.³ A threshold of BVL of >0.4% per year was defined as significant loss relative to the rate of BVL in healthy volunteers (0.1%–0.3%) vs untreated patients with MS.³ A few studies^{6–10} have reported an association of NEDA-4 with no long-term disability progression. The results have been variable and have not been summarized. Moreover, it is unclear how NEDA-4 and NEDA-3 compare in their association with no disability progression in people with RRMS over a long-term follow-up. This understanding is essential to inform use of NEDA as an outcome for treatment response in therapy trials and clinical practice, as suggested by American Academy of Neurology and European Academy of Neurology guideline committees.^{11,12}

The primary objective of this systematic review and meta-analysis was to summarize the evidence on the association between NEDA-4, as measured in the first 1–2 years after DMT initiation, and no long-term disability progression as assessed at a minimum of 4 years from baseline. Our secondary objective was to compare NEDA-4 and NEDA-3 for their associations with no long-term disability progression, where both were tested in the same cohort.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses methodology.¹³ The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42020189316). This study was exempt from ethics board review approval as a systematic review and meta-analysis.

Eligibility Criteria

Types of Studies

We included studies of patients with a minimum of 4 years of follow-up after DMT initiation. Eligible study designs

included cohort and clinical trial extension studies. For the primary objective, studies were required to report the association of NEDA-4 vs evidence of disease activity (EDA)-4 at the last follow-up, or for these data to be derivable. If data were not available or could not be derived, they were requested from the authors through at least 2 email communications. The cohort with a longer follow-up was selected where there were overlapping cohorts. For the secondary objective, studies were required to report data on both NEDA-4 and NEDA-3, or for these to be derivable, and to have a minimum of 4 years of follow-up with data on progression reported after a full follow-up. We excluded case reports, editorials, and review articles.

Population

We selected studies that included patients with RRMS. Patients with progressive MS and those with clinically isolated syndrome were allowed to comprise up to 20% of the cohort; however, all the included studies enrolled only patients with RRMS.

Literature Search

Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched for English language studies published from January 1, 2006, until November 19, 2021. For MS, we searched using the MeSH “demyelinating disease” and the Emtree subject heading “multiple sclerosis” and the key words “multiple sclerosis.” Because NEDA is a codified concept, we used natural language: “disease-free status,” “disease-free activity,” “no evidence of disease activity” or “NEDA” in the title. We also used reference lists of identified articles and systematic review studies as additional sources for primary studies. At least 2 investigators (D.R. and J.S., A.M., G.S., or D.D.) independently screened titles and abstracts for initial eligibility and evaluated full-text articles in duplicate for final inclusion. Disagreements were resolved by discussion, which included a third author (P.S.).

Exposure (Test)

NEDA-4 and NEDA-3 assessment was required at 1 or 2 years from baseline after DMT initiation. For NEDA-4, the following 4 criteria were mandatory: (1) no clinical relapse, (2) no confirmed disability progression, (3) no new or enlarging T2 lesion on brain MRI, and (4) no BVL $\geq$ 0.4% per year. For NEDA-3, only the first 3 former criteria were mandatory. Often, absence of any T1 gadolinium-enhancing (gad+) lesion was included in NEDA-3 and NEDA-4, but this was not required because some studies did not involve gad-enhanced MRIs.

Outcome

The outcome was no confirmed disability progression over a follow-up of a minimum of 4 years. Most often, this was identified using 6-month confirmed disability progression (6m-CDP) as measured by EDSS change of 1.0. Some studies stipulated a change of at least 1.5 if baseline EDSS was zero and/or 0.5 if baseline EDSS was >5.0. Other permitted definitions included not reaching EDSS milestone of 6.0 or secondary progressive MS (SPMS) or death. For the randomized controlled trial (RCT) extension studies, where possible, we evaluated only the treatment arms of approved doses as indicated.

Data Extraction and Covariates

Two authors (D.R. and J.S.) used a predesigned data collection form to independently extract study details that were then checked together. Baseline cohort characteristics were collected based on published description of the intention-to-treat clinical trial population or observational cohort.

Risk of Bias Assessment

We used the Quality in Prognosis Studies tool to evaluate the risk of bias.¹⁴ Six domains are considered in the risk of bias assessment (eTable 1, links.lww.com/NXI/A745). Domains were each rated as a low, medium, or high risk of bias. Studies were classified as overall low risk of bias if all domains were rated as low risk, and high risk of bias if one or more domains were rated as high risk.

Analysis

For the primary objective, we used a random-effects model to synthesize the pooled odds ratio (OR) with 95% confidence interval (CI) for no disability progression with NEDA-4 vs EDA-4. If

the OR was not reported in the published manuscript, then it was calculated from the 2×2 table. Heterogeneity was evaluated using the I^2 statistic. We also evaluated the pooled ORs separately by DMT class. We performed a sensitivity analysis excluding 1 study⁶ due to differences in definition of the outcome and duration of follow-up, which was much longer than the other included studies.

For the secondary objective, we included studies that reported both NEDA-4 and NEDA-3. To assess the difference between the degree of association of NEDA-4 with the outcome and NEDA-3 with the outcome, we estimated the difference between the log OR of outcome (NEDA-4 vs EDA-4) and log OR of outcome (NEDA-3 vs EDA-3). Then, we converted back to the ratio of ORs to assess whether ORs were significantly different between NEDA-4 vs EDA-4 and NEDA-3 vs EDA-3. Data management and all statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and “meta” “mada” R package in R 4.0.0 (r-project.org).

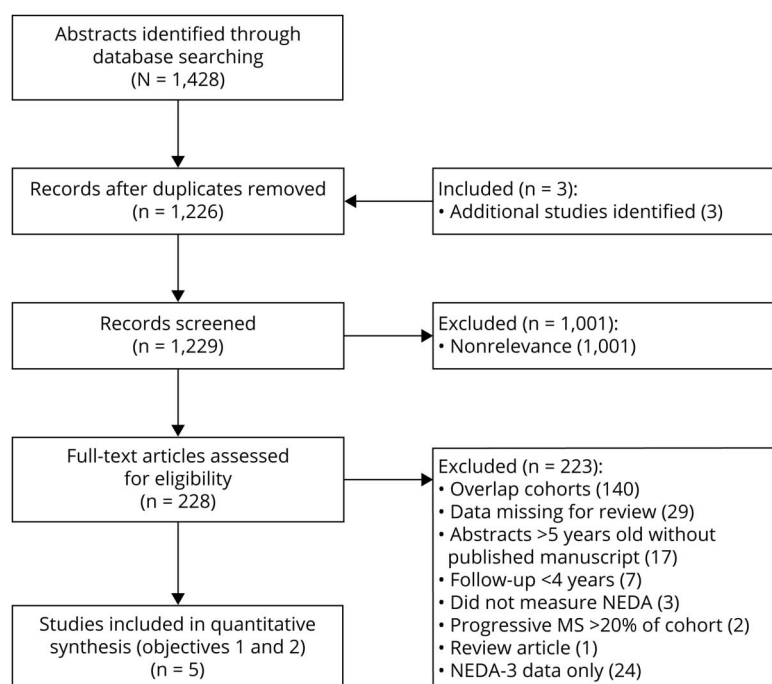
Data Availability

Data not published within this article will be made available on reasonable request to the corresponding author from any qualified investigator.

Results

Five studies including 1,000 participants met inclusion criteria for the primary objective (Figure 1). The same 5 studies were selected for analysis of the secondary objective because all reported data for NEDA-3 in addition to NEDA-4. The

Figure 1 PRISMA Flow Diagram for Study Selection



PRISMA flow diagram showing study selection and reasons for omission of excluded studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Baseline Characteristics of Included Studies

Source, location (years of recruitment)	Study design (name of study or cohort, if given)	Therapies studied	% on given therapy	Number enrolled/ number followed	Duration of follow-up (y)	Baseline mean age (y)	Female (%)	Baseline median EDSS	Baseline mean disease duration (y)	ARR before study	Overall risk of bias rating (reason, if medium or higher risk)
Cohen et al.,^{9,10} International (2006–2007)	RCT Extension (TRANSFORMS), multicenter	FTY ^a	100	429/232	6	36.7	65.4	2.0	7.5	1.5	High (attrition)
Goodin et al.,⁶ 2019 USA, Canada (1988)	RCT Extension (IFNB Multiple Sclerosis Study Group), multicenter	IFNB-1b Placebo	68.6 31.4	376/215	16	35.2	69.0	2.5	7.7	1.7	High (attrition)
Kappos et al.,^{10,15} 2015 International (2006–2007)	RCT Extension (FREEDOMS), multicenter	FTY ^a	100	425/341	6	36.6	69.6	2.0	8.0	1.5	Low
Perez-Miralles et al.,⁸ Spain (2001 onwards)	Retrospective single center cohort (Barcelona cohort)	IFN	100	124/101	4	34	80.2	1.5	3.0	1.5	Low
Srpova et al.,⁷ Czech Republic (2005–2009)	Prospective multicenter cohort (SET)	IFN	100	220/166	4	29	66.9	1.5	0.2	N/A	Medium (attrition)

ARR = annualized relapse rate; EDSS = expanded disability status scale; FTY = fingolimod; IFN = interferon beta; IFNB-1b = interferon beta-1b; RCT Ext = Randomized Controlled Trial Extension.

^a 0.5 mg treatment arm only.

median duration of follow-up was 6.0 years (range: 4–16 years) (Table 1). Three of the included studies investigated participants on interferon beta therapy or placebo.^{6–8} Of these, 2 were observational studies,^{7,8} and one was an RCT extension study.⁶ The other 2 included studies were the extension cohorts from the fingolimod clinical trials.^{9,10,15} Two studies had a low risk of bias,^{8,15} one had a medium risk of bias,⁷ and 2 had a high risk of bias,^{6,9} with a higher risk of bias primarily due to attrition. All but one⁸ were multicenter studies.

Baseline cohort characteristics varied across studies including mean age (29–36.7 years), percentage of female participants (66%–80%), median or mean EDSS (1.5–2.5), disease duration (0.2–8 years), and annualized relapse rate (1.5–1.7) (Table 1). Four studies evaluated NEDA at 2 years after initiating therapy and 1 study⁸ evaluated NEDA at 1 year (Table 2). Four studies used no 6m-CDP as their outcome at the end of follow-up. One study⁶ used conversion to SPMS or reaching an EDSS ≥ 6.0 or death to evaluate disability progression at the end of follow-up.

NEDA-4 was met by 4.2%–13.9% on interferon beta therapy and 24.9%–25.1% on fingolimod therapy (Table 2). NEDA-3 was met by 8.8%–34.7% of those on interferon beta therapy and 34.1%–37.2% of those on fingolimod therapy.

Primary Outcome: No Disability Progression With NEDA-4

The pooled OR for no disability progression with NEDA-4 vs EDA-4 was 2.14 (95% CI: 1.36–3.37; $I^2 = 0$; Figure 2). For the

subgroup analysis stratified by DMT class, NEDA-4 was associated with no disability progression for both interferon beta (OR: 1.81; 95% CI: 0.72–4.56; $I^2 = 0$) and fingolimod (OR: 2.20; 95% CI: 0.88–5.53; $I^2 = 68\%$) therapies, but these associations did not meet statistical significance.

In the sensitivity analysis, excluding the beta interferon-1b extension study, which differed in its definition of the outcome and had a much longer follow-up than the other included studies, the pooled OR for no disability progression with NEDA-4 vs EDA-4 was 2.12 (95% CI: 1.12–3.40; $I^2 = 21\%$).

Secondary Outcome: No Disability Progression With NEDA-4 vs EDA-4 and NEDA-3 vs EDA-3

The ratio of OR for NEDA-4 vs EDA-4 and OR for NEDA-3 vs EDA-3 (OR: 0.71, 95% CI: 0.39–1.30) was not statistically significantly different in the meta-analysis and when evaluating interferon beta (OR: 0.88, 95% CI: 0.29–2.71) and fingolimod (OR: 0.65, 95% CI: 0.32–1.33) therapy studies separately (Figure 3).

Discussion

In this systematic review and meta-analysis, we identified an association between NEDA-4 and no long-term disability progression in RRMS. NEDA-4 at a median of 6 years of follow-up was associated with a 2 times higher odds of no disability progression than EDA-4. As expected, with the

Table 2 Definitions and Data Concerning NEDA-4 and NEDA-3 From Included Studies

Source	Definition of NEDA	Definition of long-term disability progression	NEDA-4 or NEDA-3	Number (%) with NEDA	Number with NEDA and no disability progression	Number with NEDA and disability progression	Number with EDA and no disability progression	Number with EDA and disability progression
Cohen et al.,^{9,10} 2016	2 y, gad+ lesions included	6m-CDP ^a	NEDA-4	58 (25.1%)	48	10	135	38
			NEDA-3	79 (34.1%)	68	11	116	37
Goodin et al.,⁶ 2019	2 y	SPMS or EDSS ≥ 6.0 or death	NEDA-4	7 (4.2%)	5	2	83	78
			NEDA-3	19 (8.8%)	12	7	91	105
Kappos et al.,^{10,15} 2015	2 y, gad+ lesions included	6m-CDP ^a	NEDA-4	83 (24.9%)	73	10	170	81
			NEDA-3	127 (37.2%)	115	12	135	79
Perez-Miralles et al.,⁸ 2020	1 y, gad+ lesions included	6m-CDP ^a	NEDA-4	11 (10.9%)	N/A ^c	N/A	N/A	N/A
			NEDA-3	35 (34.7%)	N/A ^c	N/A	N/A	N/A
Srpova et al.,⁷ 2021	2 y, gad+ lesions included	6m-CDP ^b	NEDA-4	23 (13.9%)	21	2	118	25
			NEDA-3	39 (23.5%)	34	5	105	22

CDP = confirmed disability progression; EDA = evidence of disease activity; EDSS = expanded disability status scale; NEDA = no evidence of disease activity; SPMS = secondary progressive multiple sclerosis.

^a 6m-CDP = Change in EDSS of at least 1.0 if baseline EDSS 0–5.0, 0.5 if baseline EDSS >5.0 .

^b Change in EDSS of at least 1.0 if baseline EDSS 1.0–5.0, 1.5 if baseline EDSS 0, and 0.5 if baseline EDSS >5.0 .

^c Odds ratios were reported in the paper but not numbers for NEDA/EDA vs disability progression.

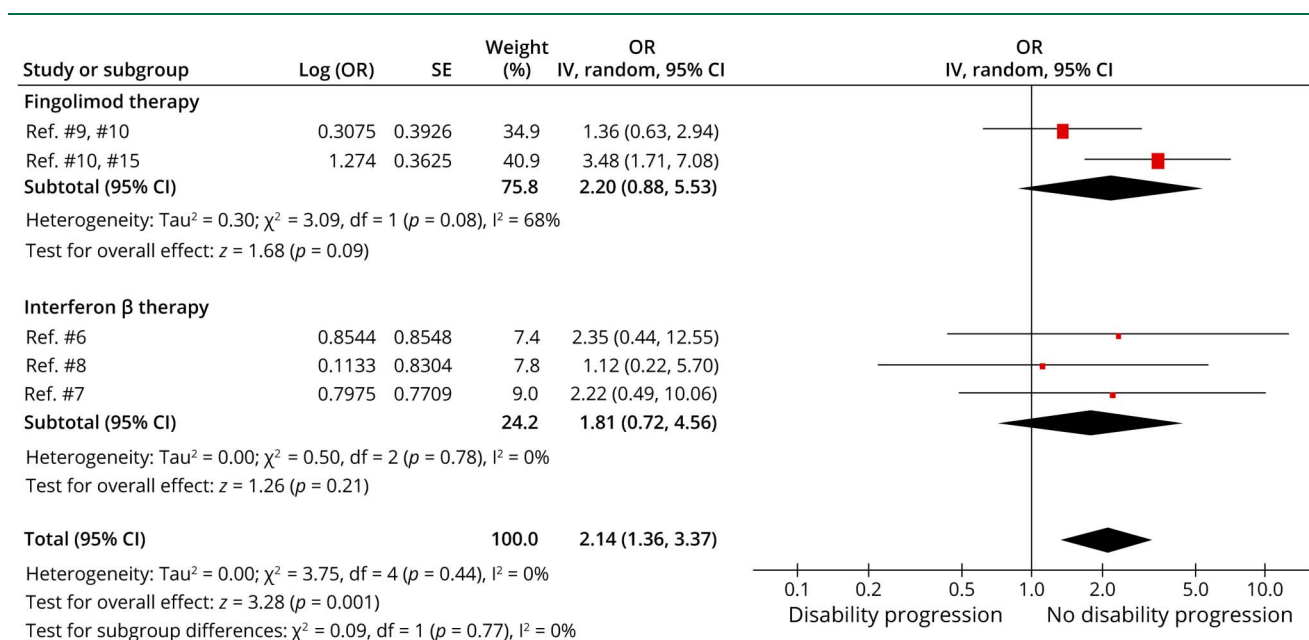
addition of a brain atrophy measure on top of the criteria required for NEDA-3, a lower proportion in each study met NEDA-4 vs NEDA-3. Comparing NEDA-4 with NEDA-3, there was no significant difference between these 2 composite outcome measures in predicting disability progression, although power was limited by the small number of studies ($n = 5$) and relatively small number of participants ($n = 1,000$) across studies.

In a larger systemic review and meta-analysis of 27 studies that we previously conducted investigating NEDA-3, we found pooled ORs of 2.32 (95% CI: 1.58–3.42; $I^2 = 73\%$) on low-efficacy therapy and 3.19 (95% CI: 1.86–5.47; $I^2 = 86\%$) on high-efficacy therapy for the association of NEDA-3 with no long-term disability progression.¹⁶ In this review, we performed subgroup analyses by DMT type (interferon beta and fingolimod), with pooled ORs in similar ranges, although the results did not meet statistical significance, which was likely due to power limitations. The ORs for the association between NEDA-4 and no long-term disability progression were greater than 1 in each of the included studies, but results reached statistical significance in only 1 study. Where relatively low proportions of individuals achieve a composite outcome measure such as NEDA-4, larger studies and reviews such as this may be necessary to better understand predictive capabilities.

There is a great unmet need for evidence-based composite outcome measures assessed in the first years on therapy,

which can accurately predict long-term prognosis in RRMS. The historic tradition of using relapse rate as a primary outcome for DMT efficacy is arguably of less relevance in the modern era of early MS diagnosis and treatment when annualized relapse rates in clinical trials are typically less than 0.4¹⁷ and as low as 0.10.¹⁸ Composite outcome measures are more sensitive to different aspects of disease activity. They also reflect our ability to aim for a higher standard of disease control with second-generation, high-efficacy DMT. NEDA-3, however, has been criticized for overly emphasizing focal inflammatory activity, with the CDP criterion being the sole proxy for neurodegenerative aspects of MS.¹⁹ In some real-world cohorts, a considerable share of those with NEDA-3 at 2 years demonstrated disability progression at a long-term follow-up.^{6,20} For example, in the extension study of the randomized trial of interferon beta-1b, which was included as part of this meta-analysis, 37% of those with NEDA-3 at 2 years had negative disability outcomes at 16 years of follow-up, although numbers were small (19 with NEDA-3). In an Italian cohort study of patients with RRMS who were started on interferon beta or glatiramer acetate, which did not qualify for this review because of lack of NEDA-4 data, 26% (58/224) of those with NEDA-3 over 2 years had subsequent disability accrual by a median of 12 years of follow-up.²⁰ Notably, both these studies involved a follow-up of more than 10 years. In the subgroup of patients who demonstrated long-term disability progression independent of relapse activity (PIRA), MRI activity was also uncommon (11%), suggesting the need

Figure 2 Association of NEDA-4 vs EDA-4 With No Long-term Disability Progression



ORs were assessed for each study for the association of NEDA-4 vs EDA-4 with no long-term disability progression. NEDA-4 was defined by (1) no clinical relapse, (2) no confirmed disability progression, (3) no new or enlarging T2 lesion on brain MRI, and (4) no brain volume loss $\geq 0.4\%$ per year. Pooled ORs were evaluated for each therapy group (interferon beta and fingolimod) and across all studies. EDA = evidence of disease activity; NEDA = no evidence of disease activity; OR = odds ratio.

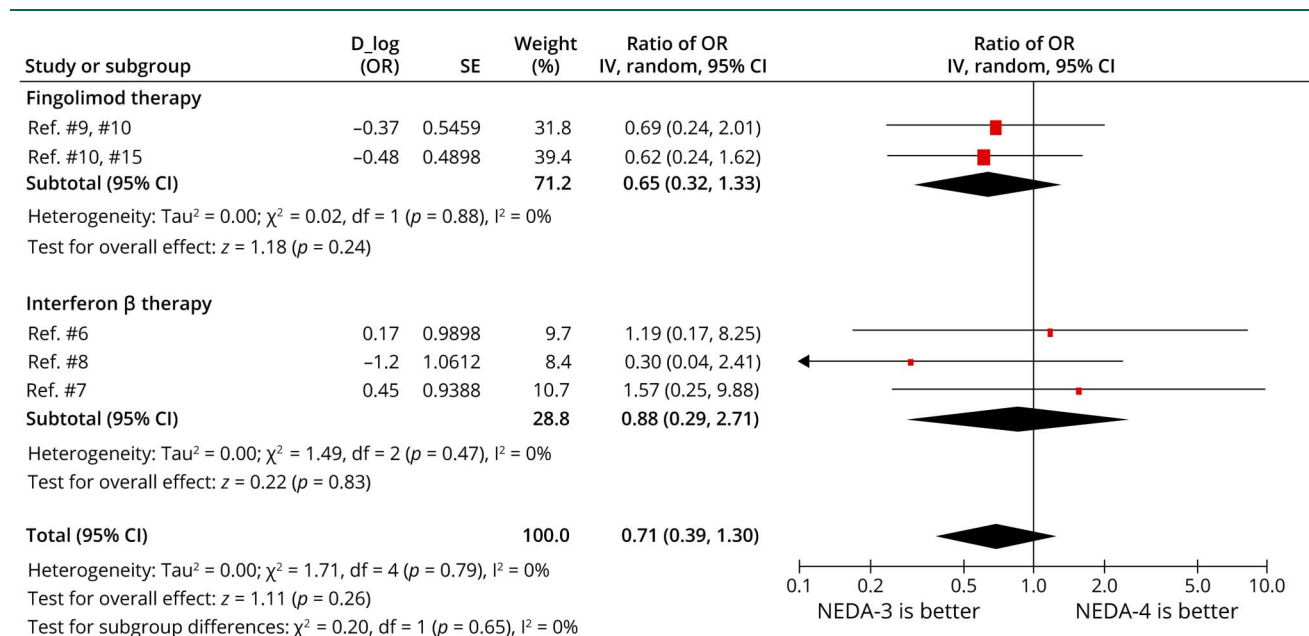
for other early biomarkers to capture this group of RRMS patients with poorer prognosis.²⁰

NEDA-4 was introduced in 2016 based on post hoc analyses of the fingolimod treatment trials.³ The promise of NEDA-4 was that inclusion of BVL, a marker of neurodegeneration, might better predict the long-term disability trajectory on a given therapy. BVL is known to occur in the earliest stages of MS,²¹ and gray matter atrophy has been associated with clinical worsening over both the short-term²² and long-term.^{4,5} Challenges of incorporating BVL into an early composite outcome measure include limited availability of brain volume assessment at many clinical centres; limited reproducibility of exact BVL measurements across centres and methods; vulnerability of brain volume changes to other factors, including hydration status and use of corticosteroids; variable rates of BVL depending on age at MS onset and MS disease duration; and a pseudoatrophy effect in the first year on certain DMT, such as natalizumab.²³⁻²⁵ The findings in this meta-analysis suggest that NEDA-4 does not offer superior prognostic value compared with NEDA-3 and thus may not warrant the extra effort and cost required for its routine evaluation in clinical practice, although these findings need to be confirmed in other cohorts with extended longitudinal follow-up. In the meantime, NEDA-4 may be most relevant as an outcome measure in the clinical trial context, in which BVL measurement is more readily supported. Overall, NEDA, whether NEDA-3 or NEDA-4, can be taken as an indication that a patient is a good responder to therapy. However, it is important to note that there are some patients with NEDA

who demonstrate progression long-term, which is often PIRA, and at this point, it is unclear whether a switch in therapy could ameliorate long-term outcomes in these patients.

Ongoing research is investigating other candidate measures that could be used in combination with NEDA or in an evidence-based scoring system to evaluate optimal responders over the first years on DMT. These include serum or CSF biomarkers such as neurofilament light chain (NfL) and glial fibrillary acid protein, cognitive measures, MRI assessment of smouldering or cortical lesions, and optical coherence tomography measures such as retinal nerve fiber layer or ganglion cell/inner plexiform layer thinning. One study found that a composite measure of NfL levels over 2 years, clinical and MRI measures, led to greater prognostic value (as measured by area under the receiver operating curve) for long-term outcomes at 7 years compared with models with NfL, clinical and MRI predictors alone or in any other combination.²⁶ Another shortcoming of current definitions of NEDA is that many of those with EDA do well over long-term follow-up, and therefore, EDA alone seems insufficient to justify changes in therapy.¹⁶ A recent study reported that low serum NfL could predict those with EDA-3 who would be free of disease activity in the subsequent year.²⁷ It could also predict those with NEDA-3 who would have disease activity and/or brain atrophy in the following year, although high NfL levels were rare (9.4%) in NEDA-3.²⁷ A key consideration in applying NfL or any other biomarker to a predictive algorithm with NEDA should be its ability to flag the subgroup of people with RRMS who have indolent progression over the long-term but are stable for NEDA-3 in the first years on therapy.

Figure 3 Ratio of ORs for No Disability Progression With NEDA-4 vs EDA-4 Compared With NEDA-3 vs EDA-3



The ratio of ORs was evaluated for each study for the association of no long-term progression with NEDA-4 vs EDA-4 compared with NEDA-3 vs EDA-3. NEDA-3 was defined by (1) no clinical relapse, (2) no confirmed disability progression, and (3) no new or enlarging T2 lesion on brain MRI. For NEDA-4, no brain volume loss $\geq 0.4\%$ per year was required in addition to the former criteria for NEDA-3. Pooled ratios were evaluated for each therapy group (interferon beta and fingolimod) and across all studies. A ratio of greater than 1 would imply a stronger association of NEDA-4 vs EDA-4 with no long-term disability progression compared with NEDA-3 vs EDA-3. EDA = evidence of disease activity; NEDA = no evidence of disease activity; OR = odds ratio.

Limitations of this review include the small number of studies assessing NEDA-4 ($n = 5$). As mentioned earlier, NEDA-4 is not assessed routinely in observational studies because of the requirement of BVL measurement, and the minimum follow-up of 4 years reduced the number of qualifying studies, although necessary for the determination of long-term progression. Follow-up was 6 years or less in 4 of the 5 included studies, but an extended longitudinal follow-up of 10 years or more may be necessary for accurate long-term prognostication in RRMS.^{28,29} Thus, further studies of NEDA-4, NEDA-3, and other iterations of NEDA with an extended follow-up would be helpful. Study quality varied, with a higher risk of bias, notably due to attrition over time. In addition, there may be selection bias in clinical trial extension studies with preferential retainment of participants with favorable outcomes. Some heterogeneity was observed in the baseline cohort characteristics, although mean age, proportion of female participants, and baseline median EDSS were quite similar across studies. Similarly, some heterogeneity was observed in definitions of NEDA-4, NEDA-3, and the outcome measure of no disability progression. One study⁶ excluded gad+ lesions from the MRI component of NEDA and had a different definition of the outcome, but a sensitivity analysis removing this study did not change the results. While 6m-CDP was the most commonly used outcome measure across studies, sustained disability progression or attainment of certain disability milestones (e.g., EDSS 4.0 or 6.0) may be more meaningful indicators of long-term disability evolution.¹⁹ We could not evaluate characteristics of those with NEDA-4 vs EDA-4 because these data were not available for most of the studies.

In this systematic review and meta-analysis, NEDA-4, compared with EDA-4, was associated with twice the odds of no disability progression after a median of 6 years from DMT initiation in RRMS. We did not observe any difference between NEDA-4 and NEDA-3 in their association with no long-term disability progression. However, due to the small number of studies and limited duration of follow-up, risk of bias, and heterogeneity in definitions, further studies are necessary. In addition, other early composite measures incorporating novel biomarkers may be able to improve on the prognostic value of NEDA-4 and NEDA-3 in early RRMS and warrant further investigation.

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Appendix (continued)

Name	Location	Contribution
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