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A fully automated online fatigue management program for patients with multiple sclerosis: A randomized controlled trial

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Abstract

Objective: Fatigue is a major disabling symptom in many chronic diseases including multiple sclerosis (MS) but treatment options are limited. We developed a fully automated, interactive, online fatigue management program (ELEVIDA) based on principles of cognitive behavioral therapy (CBT) and related psychotherapeutic approaches (e.g. mindfulness) and tested its effectiveness for reducing fatigue in MS.

Methods: Patients with MS and self-reported fatigue were recruited via the website of the German MS Society and assigned via an automated randomization generator (1:1, no blocking or stratification) to a 12 week online intervention (ELEVIDA, n=139, 82% female, mean age 40.8, median PDDS 3.0) or a standard-care control group (n=136, 79% female, mean age 41.9, median PDDS 3.0). The primary outcome was the Chalder Fatigue Scale. Outcomes were assessed at baseline, at week 12 (post intervention), and at follow-up (week 24).

Results: Compared to the control group, significantly greater reductions in Chalder Fatigue Scale scores were seen in the ELEVIDA group at week 12 (primary endpoint, intention-to-treat analysis: between group mean difference 2.74 points; 95% CI 1.16; 4.32; p=0.0007; effect size d=0.53), with effects sustained at week 24 (intention-to-treat analysis: between group mean difference 2.19 points; 95% CI 0.57; 3.82; p=0.0080).

Conclusions: Our trial provides evidence for the effectiveness of a fully automated, internet-based intervention to reduce fatigue in MS. Interventions such as ELEVIDA may be a suitable low-barrier, cost effective treatment option for MS fatigue.

Trial registration number: The trial was prospectively registered with the ISRCTN registry (number ISRCTN25692173).

INTRODUCTION

Fatigue is a common and disabling symptom in many neurological disorders such as stroke¹, traumatic brain injury², Parkinson's disease³ and others. In patients with multiple sclerosis (MS), fatigue affects up to 70% of patients⁴ and more than three quarters of these describe it as their most disabling problem⁵. Importantly, fatigue is one of the most frequent causes for MS-related retirement⁶ and there is an association with depression⁷ and cognitive impairment⁸.

Despite the immediate clinical importance, treatment options for MS-fatigue are limited (for a systematic review, see⁹). Meta-analyses found no conclusive evidence for pharmacological treatment¹⁰. In contrast, the potential benefit of non-pharmacological interventions has been supported by several meta-analyses¹⁰⁻¹³. Cognitive behavioral therapy (CBT)-based approaches have been shown to be particularly effective in reducing MS-related fatigue (e.g.¹⁴), which has also been confirmed by meta-analyses^{10 15}.

However, there is a paucity of large RCTs in this area. Moreover, standard behavioral treatments may not be suitable for all MS patients: For example, mobility impairments may interfere with patients' ability to regularly travel to the therapist's office. In addition, MS-related symptoms such as cognitive dysfunction or fatigue itself may make it difficult for patients to complete standard length, weekly sessions with a therapist. Finally, most of these approaches require well-trained professionals and supervision. Cost constraints may prevent implementation on a large scale or in rural areas, where therapists might not be available. Given the specific needs and requirements of MS patients, internet-based approaches could be particularly well-suited for delivering behavioral interventions to this patient population. Indeed, two small pilot RCTs in the UK and New Zealand have shown promising results for an internet-based version of a CBT-program for MS-fatigue with either added telephone or email-support^{16 17}. We thus conducted a large RCT of a novel internet-based treatment approach and examined its effectiveness for MS-related fatigue.

METHODS

Study Design and Population

This was a parallel group, two-arm, randomized controlled trial of a 12-week, internet-based, CBT intervention (ELEVIDA). Patients were automatically randomized to ELEVIDA or standard care control group after completing baseline outcome measures (week 0). Follow-up of outcomes was obtained at week 12 (directly after the end of the intervention), and week 24 (long term follow-up).

A decision framework for appropriate control conditions for clinical trials examining behavioural interventions has recently been published¹⁸. According to this decision framework, participation risk for our patients was low and there is a paucity of evidence from large clinical trials in MS fatigue in general and for the efficacy of online-based therapeutic options for MS-related fatigue in particular. Thus, a standard care control group was deemed appropriate for the current stage of development for ELEVIDA¹⁸. Participants randomized to the standard care control condition were provided with access codes to ELEVIDA after completing the week 24 assessments.

The trial was approved by the ethics review committee of the Hamburg Chamber of Physicians (review number PV4772) and registered with the ISRCTN registry prior to patient enrolment (registration number ISRCTN25692173).

Patients were recruited by advertisements published on the website of the German MS patient organisation (Deutsche Multiple Sklerose Gesellschaft DMSG), both by the local DMSG chapter as well as nationally. In addition, information about the study was sent out via the e-newsletter of the INIMS and leaflets were distributed at the MS outpatient center, University Medical Center Hamburg-Eppendorf.

Inclusion/exclusion criteria

Patients were eligible if they had a diagnosis of MS^a, were at least 18 years of age, reported fatigue at screening (as indicated by a score of 43 or higher on the Fatigue Scale of Motor and Cognition; FSMC;¹⁹), reported no major neurological or psychiatric comorbidities (dementia, stroke, autism, or psychosis, although comorbid depression was allowed), and no MS relapse in the last 4 weeks.

Randomization and Masking

After completing the last page of the online questionnaire, patients were randomly allocated (1:1, no blocking or stratification) to ELEVIDA or to the waiting control group using a fully automated computer algorithm (concealed allocation). For the randomization, the EFS Survey platform used a random number generator built into the system to assign patients to one of the two groups (ELEVIDA or standard care control). To complete assessments 12 weeks and 24 weeks after randomization, participants were invited via standardized emails at predefined times (3 reminders within 4 weeks each) by one of the study investigators (JP). All outcome measures were collected via an automated online interface.

^a To verify that participants had a clinical diagnosis of MS, half of the patients were randomly selected by the EFS platform and were requested to send written confirmation of their diagnosis (letter signed by their neurologist or copies of their medical records by email, mail, or fax). Of the selected patients, 90.2% provided the requested confirmed diagnosis. The minimum required fatigue score and the full list of excluded neurological and psychiatric comorbidities were unknown to the patients when they completed screening and eligibility assessment.

Procedures

Program development: The ELEVIDA program was jointly developed by a multidisciplinary team of physicians, psychologists, psychotherapists and IT experts. Details about the development process can be found in Supplementary Materials. The program was made available at no cost for patients in this trial. In ELEVIDA, content is based on cognitive behavioral therapy (CBT) strategies and is conveyed chiefly via the technique of a “simulated dialogue”. Program modules are comprised of an introduction and a summary and include homework tasks. Patients are advised to access the program once to twice per week. Participants are invited to respond continuously to narrative text passages provided by the program using a multiple-choice format. Depending on patients’ responses, the program tailors subsequently offered information to match the individual needs (e.g., preference for elaborated explanations, additional exercises, shorter texts, etc.).

Clinical descriptors

All clinical and demographic descriptors were assessed by self-report from the patients via online questionnaires. The disability ratings were derived from the Patient Determined Disease Steps (PDDS) instrument²⁰. It has been shown that the PDDS correlates highly with EDSS scores rated by experienced neurologists, objective tests of walking ability such as the 6-minute walking test, and real world mobility as assessed by accelerometer measures²¹.

Outcome measures

The pre-specified primary outcome measure was the Chalder Fatigue Scale. This questionnaire assesses severity of physical and mental fatigue and is not disease specific. The scale contains 11 items covering physical fatigue (items 1-7) and mental fatigue (items 8-11). Two previous cross-sectional studies in autoimmune disorders (systemic lupus erythematosus and rheumatoid arthritis) estimated the minimally important difference for improvement on the Chalder Fatigue Scale between 0.7–1.4^{22 23}. The Chalder Fatigue Scale has good psychometric properties²⁴, has been validated in MS patients²⁵, and is sensitive to change²⁵. This is particularly important as other fatigue scales frequently used in MS such as the MFIS and the FSS have not been shown to be sensitive²⁶. Moreover, the Chalder scale is a pure measure of fatigue severity in contrast to other frequently used fatigue scales in MS such as the MFIS, which measures impact of fatigue (rather than severity) and the FSS (which is a combination of severity and impact) as demonstrated in a recent validation study²⁵. The pre-specified primary endpoint analysis listed in the registry entry was group differences from baseline to post treatment (i.e. 12 weeks after randomization) and 3 months later (i.e. 24 weeks after randomization).

Pre-specified secondary outcome measures were MS-specific motor and cognitive fatigue measured by the Fatigue Scale for Motor and Cognitive Functions (FSMC¹⁹), anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS-A and HADS-D,²⁷), health-related quality of life quantified by the Hamburg Quality of Life Questionnaire for MS (HAQUAMS^{28 29}), and self-reported cognitive difficulties as assessed by the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)³⁰. Activities of daily living as assessed by the Frenchay Activity Index (FAI)³¹ was pre-specified as an exploratory outcome. Additional questionnaires were obtained as exploratory measures (assessing illness perception, coping, and personality traits, and responses to symptoms, see trial registration) and these will be reported separately.

Statistical analyses

Sample size calculation was based on the previously published face-to-face/telephone delivered CBT intervention³² and performed using G*Power 3.1 software. Target sample size in the trial registration was 204 participants (i.e. 102 per group). Sample size was based on an estimated standardized effect size (Cohen's d) of 0.35 (given that a fully automated program would likely have smaller effects than face-to-face therapy) with significance level α set at 0.05 (one tailed) and a power of 0.80.

Continuous clinical characteristics and baseline scores are summarized by means and standard deviations. Categorical clinical characteristics are described by frequencies and percentages. Treatment effects were estimated and tested using an intention-to-treat approach as primary analysis based on multiple imputations with baseline fatigue (Chalder) and sex as predictors. The number of imputations was set to 100, which is in line with recent recommendations³³. The primary analysis model was an analysis of covariance (ANCOVA) with Chalder fatigue score at week 12 as dependent variable and intervention group as factors and baseline Chalder fatigue score as covariate. The same analysis was used for secondary endpoints.

We imputed missing scores at week 12 in the primary analysis and weeks 12 and 24 for follow-up analyses making a missing-at-random assumption. The sensitivity of our results to the missing at random assumption was explored by missing-not-at-random models including control-based pattern imputation and a tipping-point analysis shifting the expected values of the dropouts in the intervention group. We also re-ran the primary analysis in all patients with neurologist-confirmed diagnosis (n=120) as well as the subgroup who had accessed the program at least once (i.e. "modified" ITT) as sensitivity analyses. Additional sensitivity analyses included ANCOVA (change from baseline in the Chalder scale as dependent variable) with last observation carried forward (LOCF) adjusting for baseline Chalder scale

scores. Moreover, we computed the ANCOVA analysis using the complete cases sample (per protocol analysis) as well as a mixed effects model repeated measures (MMRM) analysis including all available follow-up data as further sensitivity analyses.

Treatment group differences were estimated by least-squares means and are reported with 95% confidence intervals and two-sided p-values testing the null hypothesis of no treatment difference. A p-value smaller 0.05 is considered statistically significant in the primary analysis. Secondary analyses are of an exploratory nature and were not adjusted for multiple testing.

We conducted several post hoc analyses of the data to estimate clinical relevance of the achieved effects. Following FDA guidelines for patient-reported outcome measures, we analyzed data on minimal clinically important difference (MCID) in patients' quality of life. Here, we used the Hamburg QoL Questionnaire (HAQUAMS), a validated MS-specific QoL instrument with established thresholds for clinically relevant change (threshold of 0.36 on the fatigue subscale)²⁸. As recommended by the FDA (UCM193282), we used the anchor-based MCID³⁴ and measured the treatment effect against the definitions put forth by Kieser & Hauschke³⁵. We also analyzed activities of daily living as a measure of ELEVIDA's impact on patients' every day life as measured by the Frenchay Activity Index (FAI)³¹.

Adverse events were not pre-specified but defined post hoc as an increase in fatigue by more than three points or an increase in levels of depression (HADS-D) from below to above the established threshold for clinically relevant symptoms (>8). Adverse events are described as frequencies and percentages by intervention group.

All statistical analyses were carried out using SAS version 9.4. Patient-level data for primary and secondary outcome measures are available for download online (Supplementary File).

RESULTS

Participants

Patients were enrolled from July 11, 2014 to November 28, 2014 (duration of the recruitment period: 140 days). The CONSORT flow chart is displayed in Figure 1, patient characteristics at baseline are provided in Table 1 and Table 2.

Missing data

As shown in Figure 1, the overall drop-out rate at post intervention was 19% (n=51).

Treatment adherence

During the study period, participants randomized to ELEVIDA accessed the program on average 14.5 times (SD 13.0) and had logged activity within the program for on average 16.3

different days (SD 17·1) during the intervention phase. A total of n=15 (11%) participants in the intervention group never accessed the program.

Primary outcome

Overall, fatigue levels as measured by the Chalder scale decreased in both groups but this decline was more pronounced in the ELEVIDA group (see Figure 2 and Table 3). The intention-to-treat primary analysis (multiple imputations with baseline Chalder score and sex as predictors) yielded a statistically significant treatment effect at week 12 with a mean difference on the Chalder scale of -2·74 points (95% CI -1·16; -4·32; $p=0·0007$; $d=0·53$). Numerous sensitivity analyses were conducted to confirm these results. Treatment effects were almost identical when sex was not used as a predictor in the multiple imputations model (mean difference -2·76 points (95% CI -1·17; -4·36; $p=0·0007$). We also ran the primary ITT analysis in the subgroup of 120 patients who had a neurologist-confirmed MS diagnosis. This analysis yielded a group difference of -2·50 points (95% CI -0·07; -4·93) and was still statistically significant ($p=0·043$), despite the considerably smaller sample size. When patients randomized to the treatment group who never accessed the program were excluded from the analysis (i.e. a “modified ITT analysis”), results indicated a group difference of -3·33 points (95% CI -4·92; -1·74; $p<0·0001$). Statistically significant treatment effects at week 12 were also confirmed in sensitivity analyses using LOCF (mean difference -2·04; 95% CI -0·61; -3·48; $p=0·0055$) and the per protocol analysis (mean difference -3·39; 95% CI -1·77; -5·01; $p<0·0001$).

We further investigated the sensitivity of our primary analysis to the missing at random assumption. Applying a multiple imputation procedure with control-based pattern imputation resulted in a significant intervention effect of -2·53 (95% CI (-4·14; -0·3), $p=0·0020$), i.e. only slightly smaller than the primary analysis. Furthermore, we carried out a tipping-point analysis investigating when the observed statistically significant treatment difference would turn into a non-significant result. This was done by gradually shifting the expected value of the dropouts in the intervention group. We found that the result would tip with an increase of 3·92 points on the Chalder Fatigue Scale in drop-outs. Since it appears fairly unrealistic that the response of the dropouts would differ by such a large amount, the analysis adds further support to our primary analysis. Taken together, the primary endpoint was met in the primary as well as all sensitivity analyses.

Secondary outcomes

Effects on fatigue levels at week 12 were confirmed using the secondary endpoint FSMC as well as its subscales for motor fatigue and cognitive fatigue favoring ELEVIDA (see Table 3).

There were also significant reductions on anxiety as measure by the HADS-A favoring ELEVIDA. No significant effects were seen on depressive symptoms (HADS-D) or perceived cognitive problems (MSNQ). Domain-specific QoL was significantly increased for three of the HAQUAMS subscales: Fatigue, thinking, and mobility lower extremities, favoring ELEVIDA. No significant effects were detected on QoL domains mobility lower extremities, mood, and communication. Levels of significance and confidence intervals for all secondary endpoints are presented in Table 3.

Clinical relevance of observed treatment effects

In order to address clinical relevance, we conducted additional post-hoc analyses on secondary outcomes. Anchor-based thresholds for minimally clinically important change (MCID) are the recommended way of judging clinical significance. MCID estimates are established for patients' quality of life on the HAQUAMS scale, a pre-defined secondary endpoint of our trial. The threshold for fatigue impact on quality of life measured by the HAQUAMS is 0.36 on the fatigue subscale²⁸. Here, ITT analyses indicated a "probably clinically significant effect" using published interpretation guidelines³⁵. Finally, we analyzed the impact on patients' daily lives using the exploratory endpoint activities of daily living (Frenchay Activity Index, FAI). Here, a significant increase was observed in the ELEVIDA group compared to the control group (FAI, mean difference -1.97; 95% CI -0.58; -3.35; $p=0.0053$).

Long term follow-up

Treatment effects remained statistically significant at 24 weeks (primary analysis multiple imputations: mean group difference on the Chalder scale of -2.19 points; 95% CI -0.57; -3.82; $p=0.0080$). Sensitivity analyses using LOCF (-1.53 points; 95% CI -0.09; -2.96; $p=0.0376$) and per protocol analyses (-2.87 points; 95% CI -1.20; -4.54; $p=0.0008$) were also statistically significant. Finally, long-term stability was confirmed using MMRM analysis (mean difference -2.79 points; 95% CI -1.15; -4.44; $p=0.0010$). Group differences also remained significant at 24 weeks for the secondary endpoints FSMC and both of its subscales, and HAQUAMS subscales fatigue and thinking as well as the activities of daily living (FAI) (see Table 3). However, treatment effects were no longer significant at 24 week follow-up for anxiety (HADS-A) and the HAQUAMS subscale mobility lower extremities (see Table 3).

Adverse events

For this trial, there were no pre-defined safety measures / adverse events. However, we used several measures post hoc as potential adverse events. First, we examined the number of patients who showed a reliable increase in fatigue (as determined by the primary endpoint

Chalder) of 3 points or more from baseline to post intervention (week 12). Out of all patients completing week 12 this was seen in 8 patients in the ELEVIDA group and 23 patients in the control group. An increase from below to above the clinical threshold for depression (HADS-D>8) was seen in 5 patients in the ELEVIDA group and 6 patients in the control group. For anxiety (HADS-A>8), this was observed in 6 patients in the ELEVIDA group and 11 patients in the control group. One patient randomized to the control group died during the trial for unknown reasons. He was 47 years of age and of moderate disability when he entered the study. We were not able to obtain more information about his death.

DISCUSSION

To our knowledge, this trial is the largest of any published behavioral or pharmacological fatigue treatment trial in MS to date. Beyond meeting the primary endpoint, we showed persistence of treatment benefits up to 6 months post randomization, suggesting that patients in the intervention group may have acquired new skills during the program that helped them to manage their fatigue symptoms even after they had completed the program. Moreover, we demonstrated a positive effect on activities of daily living and clinically relevant improvements in quality of life for the treatment group, which was maintained at 6 months, underscoring the robustness of our findings as well as supporting their clinical relevance. In the meta analysis by Asano & Finlayson¹⁰, exercise interventions achieved an effect size of $d=0.57$ (10 trials) and education programs (including CBT) yielded $d=0.54$ (8 trials). Another meta-analysis including all MS exercise studies that had measures of fatigue included as primary or secondary endpoints, the standardized effect size was $d=0.45$ (18 trials)¹² and the most recent meta-analysis reports a standardized mean difference of 0.53 for exercise (when analyzing 26 trials with non-exercise control conditions)³⁶. ELEVIDA in the present trial achieved an effect size of $d=0.53$. Thus, the effects of ELEVIDA are comparable to those achieved by highly structured and supervised exercise interventions and behavioral interventions delivered in person, although automated programs have much less requirements in terms of resources and infrastructure for delivery. Behavioral interventions (including ELEVIDA) thus have a better evidence base for treating MS fatigue than pharmacological treatments with amantadine and modafinil, where the meta analysis found non-significant effect ($d=0.07$; 7 trials)¹⁰. There was also inconclusive evidence for amantadine, modafinil and pemoline in a more recent meta analysis³⁷. However, it should be noted that there are individual placebo-controlled trials of other drugs including aspirin³⁸ and vitamin D³⁹, which might in the future also have a sufficient evidence base for clinical use, possibly in combination with efficacious behavioral interventions for MS fatigue.

Several limitations have to be considered when interpreting our results. First, the drop-out rate in the current trial was 19% and somewhat higher in the ELEVIDA group compared to the WLC group. This might indicate that the intervention is not equally suited for all patients or that additional tools to reduce attrition might be necessary. One possibility is that patients with more pronounced cognitive impairment might have had difficulties using the program and thus dropped out. However, self-reported cognitive complaints (as assessed by the MSNQ) were not related to treatment response (i.e. group x MSNQ interaction in an additional ITT analysis $p=0.72$). Thus, we believe (moderate) cognitive impairment is unlikely to be a major barrier for use of such programs. Attrition is a concern for any health intervention but this has to be weighted against the resources required to deliver the intervention and thus the reach and scalability of such an approach. Here, internet-based, stand-alone tools such as ELEVIDA have a clear edge over traditional delivery methods (e.g. face-to-face interventions by highly skilled therapists). Thus their public health impact can be larger even if attrition is higher than for more traditional therapies.

Disease variables (including disease course, and disability ratings) were obtained using self-report. However, MS diagnosis was confirmed by written reports from their neurologist in more than 90% of the selected patients and a sensitivity analysis restricted to this subsample yielded very similar estimates of the treatment effect (which were also statistically significant despite the smaller sample size of this analysis). It should also be noted that we did not assess sleep disorders in our patients, which often co-occur or overlap with fatigue in MS. In a related matter, we did not assess whether or not participants started any new or additional treatments (pharmacological or non-pharmacological) after enrolment. In future studies, it may thus be informative to explore effects of comorbid symptoms or possible co-interventions on treatment outcome.

Finally, our trial had no active control group. Given limited evidence for effective internet-based fatigue management programs in MS on one hand and the potential impact such easily scalable approaches would have in clinical care, we feel that the care-as-usual control group chosen here was appropriate for the current stage of development of our intervention¹⁸. Moreover, there was no indication of a nocebo response in the control group. However, the choice of control group in trials of behavioral interventions have been shown to have a pronounced effect on the observed effect size and standard care control conditions or treatment as usual typically yield the largest estimates^{18 40}. Thus, future trials evaluating ELEVIDA in MS should consider additional control conditions to separate specific and non-

specific effects of such interventions, specifically a comparison with face-to-face CBT interventions.

In conclusion, ELEVIDA and similar programs could offer an interim solution or low barrier option to help to reach patients in areas where therapists are not available or provide care to patients in settings where resources are limited.

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Björn Meyer is an employee of GAIA AG, the developer, owner, and distributor of ELEVIDA. All other authors declare no competing interests.

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FIGURE LEGENDS

Figure 1: Study design and trial profile

Figure 2: Effects of ELEVIDA on the Chalder Fatigue Scale. Mean scores (M+SEM; ITT primary analysis) are shown for the Chalder Scale before the intervention and at 12 weeks (at the end of the intervention) and 24 week follow-up. Symptoms of fatigue showed a stronger decline in the ELEVIDA group (n=139) compared to the control group (n=136) and were maintained at long-term follow-up. Group differences were statistically significant at week 12 (p=0.0007) as well as week 24 (p=0.0080).

Table 1: Clinical characteristics.

	ELEVIDA group n=139	Control group n=136
Age in years, mean (SD)	40.80 (11.1)	41.90 (9.4)
Sex (female), n (%)	114 (82.0)	108 (79.0)
Education in years, mean (SD)	14.61 (2.3)	14.91 (2.0)
Family status , n (%)		
married/living with partner	96 (70)	100 (73)
single/ divorced/widowed	43 (30)	36 (27)
Employment status (%)		
full/part time time employment	71 (51)	64 (47)
housemaker/student/other	13 (9)	11 (8)
unemployed/unable to work/retired	55 (40)	61 (45)
Disease duration in years, mean (SD)	8.91 (7.5)	9.19 (7.4)
Disease course , n (%)		
RRMS	98 (70.5)	102 (75.0)
SPMS	21 (15.1)	19 (14.0)
PPMS	8 (5.8)	3 (2.2)
Unknown	12 (8.6)	12 (8.8)
Impairment as assessed by patient determined disease steps (PDDS), n (%)		
not impaired	13 (9)	14 (10)
mild impairment	51 (37)	49 (37)
moderate impairment	27 (19)	22 (16)
walking aid/wheel chair	38 (28)	40 (29)
unclear	10 (7)	11 (8)
Disease modifying therapies (DMTs), n (%)		
none	43 (30.9)	23 (16.9)
Interferon	32 (23.0)	32 (23.5)
Natalizumab	10 (7.2)	12 (8.8)
Fumarate	19 (13.7)	17 (12.5)
Teriflunomid	2 (1.4)	3 (2.2)
Glatiramer acetate	10 (7.2)	19 (14.0)
Azathioprin	1 (0.7)	1 (0.7)
Fingolimod	12 (8.6)	13 (9.6)
Mitoxantrone	2 (1.4)	2 (1.5)
Immunoglobulins	0 (0.0)	2 (1.5)
other	8 (5.8)	11 (8.1)
Symptomatic therapies n (%)		
None	94 (67.6)	92 (67.6)
Antidepressant	33 (23.7)	28 (20.6)
Fatigue medication	1 (0.7)	2 (1.5)
Other (e.g. spasticity)	11 (7.9)	14 (10.3)

Table 2: Baseline scores of primary, secondary and exploratory endpoints. For symptom scales (FSMC, HADS, MSNQ, HAQUAMS), higher values indicate more symptoms and higher symptom impact. For activities of daily living (FAI), higher values indicate more activity. Data are provided as mean (SD).

	ELEVIDA group	Control group
	n=139	n=136
Chalder Fatigue Scale	21.58 (5.32)	21.17 (5.02)
FSMC total score	76.18 (12.55)	77.34 (11.12)
FSMC cognitive	36.78 (7.89)	37.72 (6.98)
FSMC motor	39.40 (6.33)	39.62 (5.83)
HADS anxiety	7.83 (4.17)	7.33 (3.86)
HADS depression	6.82 (4.02)	6.40 (3.61)
MSNQ	25.03 (10.62)	25.28 (9.81)
HAQUAMS fatigue	3.56 (0.88)	3.70 (0.76)
HAQUAMS thinking	3.15 (1.02)	3.33 (0.99)
HAQUAMS mobility upper	1.94 (0.90)	1.89 (0.88)
HAQUAMS mobility lower	2.80 (1.18)	2.71 (1.10)
HAQUAMS mood	2.59 (0.91)	2.46 (0.91)
HAQUAMS communication	2.42 (0.96)	2.34 (0.88)
FAI	31.56 (8.69)	31.81 (9.09)

Abbreviations: FAI: Frenchay Activity Index; FSMC: Fatigue Scale for Motor and Cognition; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire

Table 3: Effects of ELEVIDA on secondary and exploratory outcomes. Mean differences between the intervention groups (Intervention - Control) adjusted for baseline scores at week 12 and week 24 for the secondary endpoints as assessed by intention-to-treat analysis (multiple imputations). For symptoms scales (FSMC, HADS, MSNQ, HAQUAMS), negative values favor the intervention group. For activities of daily living (FAI), positive values favor the intervention group.

	Group difference at 12 wk Mean (95% CI) p value	Group difference at 24 wk Mean (95% CI) p value
FSMC	-3.47 (-5.79; -1.15) p=0.0034	-3.47 (-5.89; -1.05) p=0.0049
FSMC-cognition	-1.78 (-3.12; -0.44) p=0.0092	-2.01 (-3.38; -0.64) p=0.0041
FSMC-motor	-1.71 (-0.48; -2.94) p=0.0064	-1.49 (-2.74; -0.23) p=0.0204
HADS-A	-0.64 (-1.25; -0.03) p=0.0406	-0.71 (-1.43; 0.01) p=0.0518
HADS-D	-0.33 (-0.96; 0.29) p=0.2961	-0.50 (-1.18; 0.18) p=0.1507
MSNQ	-1.45 (-3.13; 0.22) p=0.0891	-0.27 (-2.21; 1.66) p=0.7837
HAQUAMS fatigue	-0.39 (-0.57; -0.20) p<0.0001	-0.25 (-0.44; -0.06) p=0.0111
HAQUAMS thinking	-0.17 (-0.34; -0.00) p=0.0458	-0.19 (-0.39; -0.00) p=0.0495
HAQUAMS mobility upper	-0.10 (-0.26; 0.06) p=0.2243	-0.14 (-0.29; 0.01) p=0.0715
HAQUAMS mobility lower	-0.13 (-0.26; -0.01) p=0.0397	-0.07 (-0.24; 0.09) p=0.3818
HAQUAMS mood	-0.11 (-0.27; 0.05) p=0.1848	-0.11 (-0.30; 0.08) p=0.2643
HAQUAMS communication	-0.14 (-0.30; 0.03) p=0.1074	-0.12 (-0.28 ; 0.05) p=0.1648
FAI	1.97 (0.58; 3.35) p= 0.0053	1.76 (0.20; 3.33) p=0.0275

Abbreviations: FAI: Frenchay Activity Index; FSMC: Fatigue Scale for Motor and Cognition; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire