Stress Management and Multiple Sclerosis: A Randomized Controlled Trial

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Abstract

There is a well-established adverse reciprocal relationship between stress and multiple sclerosis (MS). However, stress management in these patients has been parsimoniously studied. In this parallel randomized controlled trial, relapsing-remitting MS patients were randomly assigned to undergo either an 8-week stress management program (n = 31; relaxation breathing and progressive muscle relaxation, twice a day) or not (n = 30). Self-reported validated measures were used to evaluate perceived stress, health locus of control, anxiety, and depression. Daily diaries of MS symptoms were also kept by patients. In patients in the intervention group, perceived stress and symptoms of depression were significantly decreased after 8 weeks of relaxation. Repeated measures analyses showed significant group-by-time interactions for both the number of weekly symptoms and the mean intensity per symptom. No other significant change was reported. We deem that our results should encourage future studies that will incorporate more objective clinical and laboratory outcomes.

Keywords: Multiple sclerosis; Stress; Anxiety; Depression; Symptoms; Treatment

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system of unknown origin and unpredictable course. The treatment of MS has mainly focused on the reduction in annual relapses, disability and symptom relief, consisting of immunomodulatory, immunosuppressive, and symptomatic drug therapy. However, from MS patients’ perspective, multiple disease-related stressors, such as relapses, unpredictable neurological symptoms, treatment complexity, interpersonal relationships, daily activities, potential changes to income, and employment, lead to the symptoms of anxiety and depression and compromise the quality of life (José Sá, 2008). Furthermore, both epidemiological and basic research provides evidence for the association between stress and a poorer clinical course of MS. Thus, the detrimental effects of the aforementioned disease-related stressors on patients’ lives could be further precipitated (Artemiadis, Anagnostouli, & Alexopoulos, 2011; Heesen, Gold, Huitinga, & Reul, 2007). Moreover, there is evidence linking emotional stress with the exacerbation of neurological symptoms, mediated either by stress-induced inflammatory factors (e.g., TNFα, IFNγ), which impair the nerve conductance of demyelinated axons, or by mechanisms implicated in somatization disorders (Artemiadis et al., 2011; Harvey, Stanton, & David, 2006; Heesen et al., 2007; Smith & McDonald, 1999). As such, patients are trapped in a vicious circle of adversity, which most clinicians find difficult to manage in their everyday practice.
According to a recent review by Dennison, Moss-Morris, and Chalder (2009), a higher level of perceived stress, emotion-focused coping, and illness uncertainty or uncontrollability are strongly and consistently related to a poorer psychological adjustment to MS. Based on Folkman and Lazarus (1986), controllable stressors evoke problem-focused coping, whereas uncontrollable stressors favor emotion-focused coping. Although it is suggested that no coping type is superior than the other, problem-focused coping enhances perceived control and yields less psychological distress in MS patients (Dennison et al., 2009; McCabe, McKern, & McDonald, 2004). In particular, health locus of control (HLC) and especially a high level of external HLC have been demonstrated to be a partial mediator of the stress-illness relationship, allegedly due to more passive coping strategies implemented by individuals (Huttner & Locke, 1984). Although a high internal HLC, which is the indicative of a high level of perceived control over MS-related stressors, has been associated with better compliance to self-care, adjustment to the disease, fewer annual relapses and better prognosis, and individual and social functionality, it is the external HLC that has been found to predominate among MS patients (Brown, Tennant, Dunn, & Pollard, 2005). Overall, the perception of control seems to be crucial for effective problem-focused stress coping. Moreover, there is evidence from animal studies that there is a bidirectional relationship between the perception of control and stress system activity in the brain, indicating that less stress is correlated with more control (Maier, Amat, Baratta, Paul, & Watkins, 2006).

It is thus evident that a stress reduction in MS patients could merit benefits, such as a reduction in annual relapses, less neurological and psychological symptoms, as well as successful coping, internalized HLC, and better adjustment to the disease. Stress management may be accomplished by several methods, of which the simplest and most easily administered are relaxation techniques. We searched Scopus and Medline databases using “relaxation” or “stress management” in conjunction with “multiple sclerosis” as keywords, to identify pertinent studies. We identified 11 publications, 10 experimental studies, and 1 case report of a stress reduction through art work (Kelly, 2009). In six of these studies, stress management through education and relaxation techniques were incorporated into complex multisession programs. Most studies, except for one relating to fatigue therapy (Kos, Duportail, D’hooghe, Nagels, & Kerckhofs, 2007), showed positive results on physical and mental health, pain, coping strategies, self-efficacy, and health promotion behaviors (Barlow, Turner, Edwards, & Gilchrist, 2009; Bombardier et al., 2008; Hughes, Robinson-Whelen, Taylor, & Hall, 2006; Stuifbergen, Becker, Blozis, Timmerman, & Kullberg, 2003; Tesar, Baumhackl, Kopp, & Günther, 2003). Among the remaining four, two examined the role of progressive muscle relaxation (PMR) and autogenic training on the health-related quality of life and well-being (Ghafari et al., 2009; Sutherland, Andersen, & Morris, 2005), and the other two examined the effect of reflexology and hypnosis on general health (along with anxiety and stress biomarkers) and pain, respectively, compared with PMR (Jensen et al., 2009; Mackereth, Booth, Hillier, & Caress, 2009). The primary aim of this study is to extend the literature, by investigating, to our knowledge for the first time, the effects of relaxation breathing combined with PMR (RB-PMR) on daily MS-related physical symptoms, perceived stress, HLC, and patients’ mental health (e.g., depression and anxiety). Secondary endpoints included the identification of a putative dose–response effect, factors affecting compliance to treatment, and side effects.

Materials and Methods

Trial Design

This was a two-armed, parallel group, randomized controlled study with a 1:1 allocation ratio of MS patients to treatment or non-treatment groups and at 8-weeks of follow-up. After trial commencement, no change of the initial protocol (e.g., eligibility criteria) took place.

Participants and Procedure

The study was conducted at the outpatient neurological clinic (ONC) of Aeginition Hospital, Athens, Greece, between September 2010 and April 2011. Recruitment was performed once per week and on the same day each week. During this recruitment period, all participants provided fully informed written consent to participate in the 8-week study. The study was approved by the Aeginition Hospital Scientific and Ethics Committee and was consistent with the Declaration of Helsinki. All patients had been diagnosed with MS according to the Poser or McDonald criteria and were receiving immunomodulatory treatment (McDonald et al., 2001; Poser et al., 1983). Inclusion criteria were that patients must be 18–65 years of age, of Greek ethnicity, living in Athens, diagnosed with relapsing-remitting MS and be fully ambulatory (according to the Expanded Disability Status Scale, EDSS, score < 4; Kurtzke, 1983). Exclusion criteria during enrolment and follow-up included experiencing relapse and/or corticosteroid use within the last month, diagnosed with progressive MS (primary or secondary), use of psychotropic drugs (e.g., antidepressants, benzodiazepines, antipsychotic and cannabis, or other stimulants), practice of other
relaxation techniques (e.g., yoga, pilates, meditation, psychotherapy), and the inability to read or write. For both enrolment and follow-up assessments, the exacerbation of MS was defined as the worsening of existing symptoms or the appearance of new symptoms lasting more than 24 h, after at least 30 days of improvement or stability, not associated with fever. Finally, participants experiencing one or more of the 43 major life events (e.g., death of spouse, job loss etc.) described in the Social Readjustment Rating Scale during 8 weeks of follow-up were also excluded from the final analyses (Holmes & Rahe, 1967).

**Intervention and Related Measures**

Both the intervention and the control group were provided with identical verbal and written information concerning stress and its effects on health during the ONC visit. In the intervention group, RB-PMR was administered in the form of an audio CD, consisting of 10 min of RB and 15 min of PMR. Training and explanation of the concept of stress management took place during the first ONC visit. Patients were instructed to practice the guided RB-PMR CD twice a day for 8 weeks at home (for a maximum of 112 sessions). The RB technique is performed by taking deep diaphragmatic inspirations followed by slow prolonged expirations. RB is believed to increase parasympathetic activity eliciting the experience of alertness and re-invigoration (Jerath, Edry, Barnes, & Jerath, 2006). In the second phase of PMR relaxation, patients were guided through successive contractions and relaxations of different large muscle groups in a down-top orientation, as previously described by Jacobson (1938). In each step, the patients were encouraged to focus on the difference between tension and relaxation, thus gradually sharpening the perception of the relaxation response (Jacobson, 1938). PMR has been found to reduce perceived stress and salivary cortisol soon after the end of training (Carlson & Hoyle, 1993; Pawlow & Jones, 2005).

Compliance to daily recommended sessions was encouraged by telephone communication at the end of each week and recorded by a self-reported checklist. To provide consistency between the experimental and control groups, experienced health professionals also telephoned the control patients at the end of each week. During the telephone communication with both groups, patients were asked, using the standard open questions, to report on their physical symptoms, their mood, and their principal sources of stress during the last week, in order to increase compliance and/or reduce drop-outs and to check for any exclusion criterion (e.g., major life event or relapse). No counseling was provided during telephone communication with patients. At the end of 8 weeks, patients in the control group were rewarded for their participation in the study with a relaxation CD.

**Baseline and Outcome Measures**

*Socio-demographic and disease-related variables.* These variables included age, gender, marital status, educational status, income (low <1000, average 1000–1500, high >1500€), smoking status, and time since MS diagnosis.

**Perceived Stress Scale.** The Perceived Stress Scale (PSS) is a self-reported 14-item measure of the degree to which situations in an individual’s life are appraised as stressful (Cohen, Mermelstein, & Kamarck, 1983). For this purpose, respondents rated the frequency of their feelings and thoughts over the previous month in a 5-point Likert-type scale (from 0 = never to 4 = very often). There are seven positive and seven negative items and the total score was calculated by summing up each score after reversing all the positive items (minimum total score = 0, maximum total score = 56). Higher scores indicate the higher level of perceived stress by the individual during the last month. The PSS measurement was performed at the beginning of the trial and at the end of 8 weeks of follow-up. Good psychometric properties of this measure within the Greek population have been recorded (Andreou et al., 2011). In addition, the internal consistency of the 14-item scale for this study was also good for both the initial and final measurements (Cronbach’s α 0.82 and 0.87, respectively).

**HLC Scale.** HLC was measured using the 18-item HLC scale developed by Wallston, Wallston, and DeVellis (1978). The respondents expressed their level of agreement to 18 statements in a 6-point Likert-type scale (from 1 = strongly disagree to 6 = strongly agree). The scale is built upon three 6-item subscales, namely “internal HLC” (HLC1), “external HLC” (HLC2), and “chance” (HLC3). The internal HLC (HLC1) measures the degree in which the individual believes that he/she is responsible for his/her health status. The external HLC (HLC2) and chance (HLC3) represent the extent in which other people (such as medical doctors) or chance, respectively, are perceived by individuals as the main health determinants. After summing up answers for each subscale, higher scores indicate higher strength of each type of health belief (total score range 6–36 for each subscale). HLC measurements were made at baseline and at the end of 8 weeks. The instrument has been standardized for Greek populations (Karademas, 2009). The internal consistency for each subscale was found to be satisfactory for both the initial and final measurements (Cronbach’s α: initial, HLC1 0.76, HLC2 0.8, and HLC3 0.76; final, HLC1 0.66, HLC2 0.77, and HLC3 0.7).
State-Trait Anxiety Inventory scale. State-Trait Anxiety Inventory (STAI) scale is a 40-item self-administered scale, which is composed of two subscales: 20 items measuring situational or state anxiety (STAI-S) and 20 items for underlying or trait anxiety (STAI-T) (Spielberger, Gorsuch, & Lushene, 1970). For this study, we used STAI-T. Each item was scored from 1 to 4 with higher scores representing greater anxiety. After proper inversion of the positive items, the items were summed to give a total anxiety score (which ranges from 20 to 80). STAI measurements were made at baseline and at the end of 8 weeks. The instrument has been standardized for Greek populations (Liakos & Giannitsi, 1984). The internal consistency was found to be excellent for both the initial and final measurements (Cronbach’s $\alpha$ 0.91 and 0.9, respectively).

Beck Depression Inventory. This is a 21-item self-report questionnaire assessing the occurrence of depressive symptoms over the last week (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Items are rated from 0 to 3, with higher scores indicating a larger number of symptoms. Items referring to physical symptoms and functions (e.g., appearance, concentration, sleep, tiredness, appetite, weight, worry for physical health, and interest in sex) were excluded because they have been considered to artificially inflate depression severity in MS patients (Nyenhuis et al., 1995). The scores of the remaining items were summed to produce a total score from 0 to 39. Beck Depression Inventory (BDI) measurements were performed at the beginning of the trial period to determine baseline and at the end of the 8-week study. The instrument has been standardized for Greek populations (Donias & Demertzis, 1983). The internal consistency was found to be good for both the initial and final measurements (Cronbach’s $\alpha$ 0.81 and 0.82, respectively).

Symptoms of MS. All patients were asked to keep a diary of their physical symptoms attributed, according to their opinion, to MS. Each day and for 56 days (8 weeks), the patients described each of their symptoms, in their own words, and rated each of them on a scale of $1 = \text{very low}$, $2 = \text{low}$, $3 = \text{high}$, and $4 = \text{very high}$ for perceived intensity. The patients were encouraged to take into account both physical and psychological symptom intensity in their ratings. At their final visit, the diaries were given back to study personnel for assessment. Symptoms of headache and fatigue were excluded, because they were not deemed as MS-specific (e.g., interferon therapy or a demanding day could be the main culprits). The number of symptoms per week was calculated by summing all symptom events that had occurred during the last week. Weekly mean intensity per symptom was calculated by dividing the total intensity scores by the number of symptoms per week. All patients returned their diaries, except for one patient who lost his diary 1 day before his final visit to the ONC.

There was no change in trial endpoints after trial commencement.

Sample Size

During the intervention phase, we had assumed a large attrition rate of 30% by week 8, primarily due to increased intervention requirements. Therefore, we had anticipated needing a sample size of 74 MS patients (52 needed) to detect large effect sizes of 0.8 $SD$ with at least 80% power ($\alpha$ level = 0.05, allocation ratio = 1:1). Although the enrolled sample size was slightly smaller ($n = 73$), the attrition rate was 16.4%, yielding a final sample of 61 MS patients.

Randomization and Blinding

The MS patients deemed eligible at baseline assessment during the ONC visit were randomly assigned to either the intervention or the control group, using random numbers generated by an online generator (www.random.org). Randomization, baseline, and final measurements were not blinded. Two independent and experienced neurologists blindly performed symptom assessments according to the patient’s diary recordings.

Statistical Methods

Baseline group characteristics are presented as means, $SD$, and absolute and proportion values. For group comparisons, Pearson’s $\chi^2$, Student’s $t$-test, or the Mann–Whitney $U$-test was used according to normality (assessed by Q–Q plots and the Kolmogorov–Smirnov test). Next, intention-to-treat analysis was performed to ascertain the effects of the intervention. Changes in PSS, HLC1, HLC2, HLC3, STAI-T and BDI scores (after 8 weeks minus baseline) were used as outcomes. The changes between groups were tested by one-way analysis of covariance (ANCOVA) with baseline values as covariates. All assumptions of ANCOVA were checked. Finally, the effect size was calculated for each variable using the adjusted Cohen’s $d$ (adjusted mean difference divided by the square root of the error mean squared). In general, the effect sizes 0.8, 0.5, and 0.2 are considered as large, medium, and small, respectively. The effects of the relaxation treatment on the weekly number of symptoms and mean intensity per symptom were assessed using repeated measures ANCOVA to test for a difference.
between the experimental and the control group over time. All assumptions of repeated measures ANCOVA (e.g., assumption of sphericity) were checked. Gender was entered as a fixed factor and age, number of years of education, disease duration, perceived stress, and external and chance HLC were considered to be the most important basic covariates of symptom assessment by MS patients. Baseline BDI, STAI-T, and internal HLC scores were excluded from adjustment due to high correlation (Pearson’s $r > .5$) with PSS (for BDI and STAI-T) and external HLC (for internal HLC) that induces unwanted multicolinearity with the other covariates. The high correlation of these variables also ensures that our choice of PSS and HLC2 and HLC3, instead of BDI, STAI-T, and HLC1, will not change our principal findings. The effect size for this analysis was calculated using $\eta^2$, which indicates the amount of explained variance of the dependent variable by relaxation treatment. Secondary endpoints were addressed with simple Spearman’s $\rho$ correlation tests and either parametric Student’s $t$-test or non-parametric Mann–Whitney (for two categories) or Kruskal–Wallis (for $>2$ categories) analogs, for numerical-by-numerical and numerical-by-nominal comparisons, respectively, with times of relaxation CD practice as the dependent numerical variable. The $p$-value of significance was set at .05 for all analyses. Statistical calculations were performed using the SPSS for Windows (version 18.0.3) statistical software (SPSS Inc., Chicago, IL).

Results

The study flowchart is shown in Fig. 1. In total, 155 patients were assessed at the ONC during the recruitment period (September 2010–April 2011). Of 155 patients, 81 were not eligible to participate: 1 was too young (<18 years old), 12 were living in rural communities, 8 were given corticosteroids due to relapse, 47 were suffering from progressive types of MS, and 13 were taking various psychotropic drugs (antidepressants, anxiolytics, and marijuana). From the remaining 74 eligible patients, one male patient refused to participate due to his reluctance to practice stress management in his home. From the 37 patients who were randomly assigned into the treatment group, six had dropped-out during the follow-up, two were excluded due to relapse, and two (one man and one woman) had ceased answering telephone communication. From the remaining two patients, one man had discontinued because he was reluctant to practice relaxation in his home and in one woman psychologic distress interfered with diary adherence. Of the 36 patients in the control group, six had dropped-out, two due to MS relapse,
two due to a major life event occurrence (divorce and death of mother), one man had ceased answering telephone communication, and one woman was severely and psychologically distressed from keeping a diary of her symptoms. The last measurement assessment after the 8-week follow-up period took place in June 2011 (recruitment stopped in April 2011 after reaching a total of 74 eligible patients).

**Baseline Analyses**

Baseline characteristics are described in Table 1. Most of the participants were middle-aged, women, married, non-smokers, and with a mean of approximately 14 years of education, having low income and suffering from MS for an average of 7 years. The mean baseline measurements of perceived stress, HLC, anxiety, and depression are also presented. According to the theoretical ranges of scores described in the method section, midline scores (according to theoretical ranges) were recorded for PSS (mean 25.48 ± 7.68), internal (mean 26.49 ± 5.3) and external (mean 24.31 ± 6.79) HLC, and STAI-T (mean 45.82 ± 10.78). The mean scores for chance HLC (mean 17.49 ± 6.53) and BDI (mean 6.36 ± 4.72) were below the midline. There were no significant baseline differences between the two study groups (p > .05).

**Primary Endpoint Analyses**

Table 2 presents the adjusted mean changes of each primary outcome by the intervention group. After controlling for baseline measurements, there was a significant medium effect of stress management on reducing perceived stress—$F(1,192.6) = 5.83, p = .02$, Cohen’s $d = 0.62$. In addition, there was a medium but significant effect of stress management on reducing symptoms of depression—$F(1,96.55) = 10.95, p = .02$, Cohen’s $d = 0.53$—after controlling for the group by the baseline BDI scores interaction term, indicating that the mean differences of BDI scores by group varied with respect to the baseline BDI score (in Table 2, the means were calculated for baseline BDI = 6.36). After a visual graph assessment (Fig. 2), we can deduce that patients in the intervention group showed a larger BDI decline compared with controls, as seen when the baseline BDI scores became larger. Marginally significant effects of stress management were found for chance HLC—$F(1,61.26) = 3.99, p = .051$, Cohen’s $d = 0.51$. No significant effects of stress management were found for internal HLC, $F(1,18.3) = 1.5, p = .23$, Cohen’s $d = 0.32$, external HLC, $F(1,9.2) = 0.55, p = .46$, Cohen’s $d = 0.19$, and trait anxiety, $F(1,151.75) = 3.51, p = .07$, Cohen’s $d = 0.48$, although for the latter the intervention group was presented with a larger trait anxiety reduction compared with the controls.

**Table 1.** Baseline characteristics of the 61 multiple sclerosis participants in the study

<table>
<thead>
<tr>
<th>Main baseline data</th>
<th>Intervention group (N = 31)</th>
<th>Control group (N = 30)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>37.55 ± 9.75</td>
<td>41.97 ± 10.84</td>
<td>.1</td>
</tr>
<tr>
<td>Women (n [%])</td>
<td>25 (80.6)</td>
<td>24 (80)</td>
<td>.95</td>
</tr>
<tr>
<td>Married (n [%])</td>
<td>16 (51.6)</td>
<td>20 (66.7)</td>
<td>.35</td>
</tr>
<tr>
<td>Education years (mean ± SD)</td>
<td>14.55 ± 2.2</td>
<td>13.73 ± 3.1</td>
<td>.41</td>
</tr>
<tr>
<td>Income (n [%])</td>
<td></td>
<td></td>
<td>.93</td>
</tr>
<tr>
<td>Low</td>
<td>13 (41.9)</td>
<td>14 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>12 (38.7)</td>
<td>11 (36.7)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6 (19.4)</td>
<td>5 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Current smoking (n [%])</td>
<td>14 (45.2)</td>
<td>13 (43.3)</td>
<td>.89</td>
</tr>
<tr>
<td>Duration of disease in months (mean ± SD)</td>
<td>85.81 ± 60.38</td>
<td>87.7 ± 58.96</td>
<td>.95</td>
</tr>
<tr>
<td>Outcomes (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS score</td>
<td>26.03 ± 7.9</td>
<td>24.9 ± 7.54</td>
<td>.57</td>
</tr>
<tr>
<td>HLC1 score</td>
<td>27.42 ± 4.27</td>
<td>25.53 ± 6.12</td>
<td>.17</td>
</tr>
<tr>
<td>HLC2 score</td>
<td>24 ± 7.1</td>
<td>24.63 ± 6.56</td>
<td>.72</td>
</tr>
<tr>
<td>HLC3 score</td>
<td>17.23 ± 6.09</td>
<td>17.77 ± 7.06</td>
<td>.75</td>
</tr>
<tr>
<td>STAI-T score</td>
<td>45.52 ± 9.99</td>
<td>46.13 ± 11.69</td>
<td>.83</td>
</tr>
<tr>
<td>BDI score</td>
<td>6.74 ± 4.88</td>
<td>5.97 ± 4.59</td>
<td>.66</td>
</tr>
</tbody>
</table>

Notes: PSS = Perceived Stress Scale; HLC = Health Locus of Control (1 = internal, 2 = external, 3 = chance); STAI = Anxiety, State-Trait Anxiety Inventory (S = state, T = trait); BDI = Beck Depression Inventory.
*Frequencies tested by the Pearson’s $\chi^2$, means by the Student’s $t$-test and non-parametric Mann–Whitney $U$-test (in education years, duration since diagnosis, BDI scores).
In total, 1,292 symptoms were recorded. Examples of recorded symptoms were numbness, blurred vision, heavy legs, electricity sensations, and so on. Table 3 presents the results of the repeated measures ANCOVA test for the mean number of symptoms per week and the mean intensity per symptom per week after controlling for gender, age, education, disease duration, baseline perceived stress, and external and chance HLC. No significant time differences were noted for the number of symptoms—\( F(6.172) = 0.39, p = .89 \). However, there was a significant group-by-time interaction, \( F(6.172) = 2.13, p = .048, \eta^2 = 4.1\% \), meaning that MS patients in the intervention group and not in the control group suffered from a decreasing number of physical symptoms over time (Table 3). Regarding symptom intensity, both time, \( F(7) = 5.12, p = .001 \), and group-by-time, \( F(7) = 5.13, p = .001, \eta^2 = 46.1\% \), were found to be significant, meaning that all patients reported less intensity per symptom with time, but the decrease was significantly larger for the intervention group. Between-group effects were not significant for both analyses—for number of symptoms: \( F(1) = 0.062, p = 0.81 \) and for symptom intensity: \( F(1) = 1.061, p = 0.34 \) (not shown in Table 3). Similarly, between-participant effects for the different levels of gender and the other covariates were not significant for both analyses (data not shown).

### Secondary Endpoints and Side Effects

MS patients in the intervention group practiced the relaxation technique for a median of 59 of the 112 proposed times (range of 10–124) during the 8-week period. The lowest values were observed only in two patients who performed the relaxation CD.
significantly decreased perceived stress and symptoms of depression, with medium effect sizes recorded (Cohen’s d).

Discussion

Side effects were eliminated and spasticity was substantially reduced. Two MS patients, one with blepharospasm and one with leg spasticity, reported a worsening of symptoms, to positively assist study results, or to satisfy their neurologists. To minimize this source of bias, we had organized management and, therefore, should have shown more diligence in study requirements compared with the control group. On the other hand, patients in the intervention group would be more prone to ameliorate the final measurements or underestimate MS symptoms, to positively assist study results, or to satisfy their neurologists.

We conducted this pilot randomized controlled study to assess stress management treatment comprising of an 8-week relaxation training program (RB-PMR) in RRMS patients. Our results can be summarized as the following: (a) RB-PMR practice significantly decreased perceived stress and symptoms of depression, with medium effect sizes recorded (Cohen’s d). Concerning symptoms of depression, the benefits were found to be greater for patients showing more depressive symptoms at baseline. Additionally, marginally significant reductions in chance HLC scores were found. The trait anxiety was reduced in the intervention group, although the difference was not significant. (b) Repeated measures analyses during the 8-week follow-up revealed significant group-by-time interactions for the number of weekly symptoms attributed by the patients to MS, albeit RB-PMR training explained only a small variance (4.1%) of a symptom reduction in the intervention group. However, both time and group-by-time interaction were found to be significant for mean intensity per symptom reduction, indicating that MS patients practicing RB-PMR experienced less physical and/or psychological distress due to symptom occurrence compared with the control group. The effect size of RB-PMR was large, because its practice explained 46.1% of symptom intensity variance between groups and across the 8-week follow-up. (c) According to compliance frequencies, the majority of MS patients performed RB-PMR at least once per day and no dose–response relationship between frequencies, the majority of MS patients performed RB-PMR at least once per day and no dose–response relationship between times of practice and primary outcomes was noted. MS patients with a larger number of educational years and non-smokers showed a larger compliance to the proposed practice frequency (twice daily for 8 weeks).

It is acknowledged that this study has a number of limitations. First, our entire primary outcome measures were based on self-administered self-reports as opposed to objective clinical and/or laboratory assessments. Moreover, the number and intensity of MS symptoms measures were based on non-validated diaries which can introduce information bias, since there is always the possibility that adherence to recording symptom could be different between the two groups. We assume that the directionality of this difference should be against our study aim, because MS patients in the intervention group would benefit from stress management and, therefore, should have shown more diligence in study requirements compared with the control group. On the other hand, patients in the intervention group would be more prone to ameliorate the final measurements or underestimate MS symptoms, to positively assist study results, or to satisfy their neurologists. To minimize this source of bias, we had organized a number of limitations. First, our entire primary outcome measures were based on self-administered self-reports as opposed to objective clinical and/or laboratory assessments. Moreover, the number and intensity of MS symptoms measures were based on non-validated diaries which can introduce information bias, since there is always the possibility that adherence to recording symptom could be different between the two groups. We assume that the directionality of this difference should be against our study aim, because MS patients in the intervention group would benefit from stress management and, therefore, should have shown more diligence in study requirements compared with the control group. On the other hand, patients in the intervention group would be more prone to ameliorate the final measurements or underestimate MS symptoms, to positively assist study results, or to satisfy their neurologists.

### Table 3. Mean number of symptoms and mean symptom intensity per week, during 8 weeks of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Time</th>
<th>Group × time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intervention group</td>
<td>3.68 ± 0.93</td>
<td>3.32 ± 0.91</td>
<td>2.88 ± 0.99</td>
<td>2.39 ± 0.99</td>
<td>2.65 ± 1.06</td>
<td>2.27 ± 1.01</td>
<td>2.81 ± 0.93</td>
<td>1.97 ± 0.95</td>
<td>F (df) 0.39</td>
<td>F (df) 2.13</td>
</tr>
<tr>
<td>Control group</td>
<td>2.92 ± 0.92</td>
<td>3 ± 0.9</td>
<td>2.97 ± 0.98</td>
<td>3.15 ± 0.98</td>
<td>2.96 ± 1.05</td>
<td>2.48 ± 0.99</td>
<td>3.28 ± 0.92</td>
<td>3.75 ± 0.94</td>
<td>p = .891</td>
<td>(6.172)a</td>
</tr>
<tr>
<td>Mean intensity per</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intervention group</td>
<td>1.89 ± 0.59</td>
<td>1.99 ± 0.29</td>
<td>2.26 ± 0.53</td>
<td>1.93 ± 0.64</td>
<td>1.88 ± 0.59</td>
<td>1.75 ± 0.48</td>
<td>1.32 ± 0.44</td>
<td>0.51 ± 0.52</td>
<td>F (df) 5.12 (7)</td>
<td>F (df) 5.13 (7)</td>
</tr>
<tr>
<td>Control group</td>
<td>2.41 ± 0.38</td>
<td>2.26 ± 0.18</td>
<td>2.18 ± 0.34</td>
<td>2.04 ± 0.41</td>
<td>1.86 ± 0.37</td>
<td>2.01 ± 0.31</td>
<td>2.01 ± 0.28</td>
<td>2.56 ± 0.33</td>
<td>p &lt; .001*</td>
<td>p &lt; .001**</td>
</tr>
</tbody>
</table>

Note: Repeated measures ANCOVA adjusted for gender, age, education, disease duration, baseline perceived stress, external and chance health locus of control scores.

*The Huynh–Feldt correction of degrees of freedom (epsilon 0.882).

b $\eta^2 = 4.1%$.

c $\eta^2 = 46.1%$.

*Level of significance $p < 0.05$. 

## Discussion

only 10 and 17 times, respectively. The Spearman’s correlations of times of practice with primary outcomes were not significant (Spearman’s $\rho = -0.173$ for ΔPSS, $-0.173$ for ΔHLC1, $-0.044$ for ΔHLC2, $0.01$ for ΔHLC3, $-0.04$ for ΔSTAI-T, and $-0.166$ for ΔBDI differences, respectively). Thus, no dose–response relationship was observed. As far as compliance to treatment was concerned, among the baseline factors listed in Table 1, only patients with a large number of educational years (Spearman’s $\rho = 0.435$, $p = 0.14$) and who were non-smokers—$t(29) = -4.171$, $p < .001$—mean difference of practice times $= 39.14 ± 9.38$—were associated with better compliance to relaxation treatment instructions. As expected, no serious side effects were reported. Two MS patients, one with blepharospasm and one with leg spasticity, reported a worsening of their symptoms for a few seconds during PMR practice in the affected muscle groups. After 1 month of follow-up, these side effects were eliminated and spasticity was substantially reduced.
weekly telephone communication with patients of both groups; thus, the sense of offer was fostered in all patients by receiving attention over the phone. Finally, there are no clinically meaningful cut-offs for our primary outcomes; thus, the translation of our results to everyday clinical practice is impaired. For this reason, sample size calculation was based only for large effect sizes.

The generalization of our results is limited to fully ambulatory RRMS patients suffering for an average of 7 years from MS, as seen in a Greek ONC. There are several reasons why we chose this group of patients. First, it has been well studied that the stress–MS relationship is mediated by inflammatory mechanisms, and therefore, the stress reduction would be more meaningful in types of MS where inflammation is more prominent than neurodegeneration. Second, PMR requires muscle utilization; therefore, MS patients had to suffer little or no motor disability. This is supported by the two recorded side effects of temporary (for seconds during PMR practice) blepharospasm and leg spasticity worsening. Finally, adjustment to disease is more challenging during the first period after MS diagnosis and we thus believe that early treatment interventions should be prioritized to these MS patients groups.

As noted in the “Introduction” section, most studies for stress management in MS patients examine the effects of complex multisession programs (including two in PMR [Stuifbergen et al., 2003; Tesar et al., 2003]) or use outcomes of general physical and mental health or well-being (see “Introduction”). Thus, a “side-by-side” comparison with our own study is difficult. In one study by Ghafari and colleagues (2009), PMR training for 8 weeks and once per day resulted in significant physical and mental health improvement (as measured with SF-8), which was consistent with data obtained from our MS patients (age 20–45, EDSS < 5.5). In other studies, PMR showed similar efficacy with reflexology at reducing stress, but lower efficacy compared with hypnosis for chronic pain alleviation (Jensen et al., 2009; Mackereth et al., 2009).

In our study, the alleviation of physical MS-related and depressive symptoms by stress management could be explained in several ways. First, because physical symptoms were not objectively evaluated (thus, they could be organic and/or functional), reduction in both the number and intensity of symptoms in the intervention group may be mediated by: (a) reduction in stress-induced inflammatory molecules (such as TNFα and IFNγ nitrite oxide) that hinder the electrical conductance in the demyelinated axon (for organic physical symptoms) or (b) inhibition of limbic brain regions leading to attenuated physical symptom awareness, via the inhibitory basal ganglia-thalamocortical circuits (for functional symptoms) (Harvey et al., 2006; Smith et al., 1999). However, more positive results for symptom intensity rather than symptom occurrence may be attributed to the fact that the latter better represents lesion topography and less functional mechanisms as is presumably reflected by intensity perception.

Regarding depression, it is well established that there is a reciprocal relationship of stress and depression mediated by neurohormonal and brain functioning mechanisms (for review, see Gold & Chrousos, 1999; Liu & Alloy, 2010). In support of this, our study has shown significant changes only to these two outcomes; however, we provide no evidence for the factors that confer these changes. We should report that we have examined (by the Sobel test, data not shown) two meditational models for either differences of PSS or BDI as candidate mediators for the group effects on differences of BDI and PSS, respectively. According to our preliminary results, differences in depression scores mediate changes of perceived stress through relaxation practicing and not vice versa. However, larger samples are needed to draw more secure conclusions.

In sum, we provide evidence that stress management in RRMS patients may merit benefits of both physical and psychological well-being. Future studies should extend these preliminary findings using greater sample sizes, examining other similar techniques, and measuring more objective laboratory (e.g., biomarkers) or clinical (e.g., relapse rate) outcomes. We think that simple relaxation techniques, such as RB-PMR characterized by a higher administration and practice feasibility, should be deemed as highly cost-effective, non-pharmaceutical treatments in everyday clinical practice.

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**Conflict of Interest**

None declared.

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