Title
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Journal
Neurology, 79(5)

ISSN
0028-3878

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Publication Date
2012-07-01

DOI
10.1212/wnl.0b013e3182616ff9

Peer reviewed

A randomized trial of stress management for the prevention of new brain lesions in MS

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ABSTRACT

Objectives: This trial examined the efficacy of a stress management program in reducing neuroimaging markers of multiple sclerosis (MS) disease activity.

Methods: A total of 121 patients with relapsing forms of MS were randomized to receive stress management therapy for MS (SMT-MS) or a wait-list control condition. SMT-MS provided 16 individual treatment sessions over 24 weeks, followed by a 24-week post-treatment follow-up. The primary outcome was the cumulative number of new gadolinium-enhancing (Gd+) brain lesions on MRI at weeks 8, 16, and 24. Secondary outcomes included new or enlarging T2 MRI lesions, brain volume change, clinical exacerbation, and stress.

Results: SMT-MS resulted in a reduction in cumulative Gd+ lesions ($p = 0.04$) and greater numbers of participants remained free of Gd+ lesions during the treatment (76.8% vs 54.7%, $p = 0.02$), compared to participants receiving the control treatment. SMT-MS also resulted in significantly reduced numbers of cumulative new T2 lesions ($p = 0.005$) and a greater number of participants remaining free of new T2 lesions (69.5% vs 42.7%, $p = 0.006$). These effects were no longer detectable during the 24-week post-treatment follow-up period.

Conclusions: This trial indicates that SMT-MS may be useful in reducing the development of new MRI brain lesions while patients are in treatment.

Classification of evidence: This study provides Class I evidence that SMT-MS, a manualized stress management therapy program, reduced the number of Gd+ lesions in patients with MS during a 24-week treatment period. This benefit was not sustained beyond 24 weeks, and there were no clinical benefits.

Trial registration: ClinicalTrials.gov, number NCT00147446. *Neurology*® 2012;79:412–419

GLOSSARY

BIPS = Brief Inventory of Perceived Stress; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **Gd+** = gadolinium-enhancing; **ITT** = intent-to-treat; **LES** = Life Events Scale; **MS** = multiple sclerosis; **NNT** = number needed to treat; **RCT** = randomized controlled clinical trial; **SMT-MS** = stress management therapy for multiple sclerosis; **UCSF** = University of California San Francisco.

Accumulating evidence suggests an association between stress and disease activity in multiple sclerosis (MS).[1] Stressful life events have also been shown to precede new gadolinium-enhancing (Gd+) MRI brain lesions, a more objective measure of disease activity, by approximately 4–8 weeks.[2]

Several studies have indicated that more adaptive coping moderates the effect of stress on the development of new Gd+ lesions[3] and is associated with fewer exacerbations.[4] Cognitive behavioral stress management therapies (SMTs) teach coping skills that are aimed at enhancing a patient's ability to prevent stressful events from occurring and improving the capacity to manage their responses to those stressful events that do arise.

The primary aim of this multicenter randomized controlled clinical trial (RCT) was to examine the efficacy of a well-validated SMT for MS (SMT-MS)[5] in reducing the occurrence of new Gd+ lesions and new or enlarging T2-weighted lesions. Gd+ MRI is a marker of the

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From the Northwestern University Feinberg School of Medicine (D.C.M., B.C., J.S., L.J.), Chicago, IL; Louisiana State University Health Sciences Center School of Medicine (J.L.), New Orleans; Evergreen Hospital Medical Center (T.B.), Seattle, WA; University of California, San Francisco (T.N., R.H., D.D., D.P.), San Francisco; and San Francisco VA Medical Center (T.N., D.D.), San Francisco, CA.

Study funding: This study was funded by NICHD grant R01-HD043323.

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opening of the blood–brain barrier and is typically used as a primary endpoint in phase II trials because of its high sensitivity to ongoing MS disease activity and its association with clinical exacerbation.[6] T2-weighted MRI is also commonly used in phase II trials to identify more permanent lesions.

METHODS

Study design. This was a 48-week phase II randomized, multicenter, controlled, evaluator-blind, two-arm trial of cognitive-behavioral stress management therapy for MS (SMT-MS)[5,7] compared to a wait-list control. Treatment was provided over 24 weeks followed by a 24-week post-treatment follow-up period. Participants were enrolled at MS specialty clinics at 3 sites in the United States (University of California San Francisco [UCSF]; Evergreen Hospital Medical Center, Seattle, Washington; and the Feinberg School of Medicine at Northwestern University, Chicago, Illinois) and through local chapters of the National MS Society. It was hypothesized that participants randomized to SMT-MS would show significantly fewer new Gd+ and T2 lesions, compared to those in the control condition during the treatment period, and that improvements would be sustained over the 24-week follow-up period. This study provides Class I evidence for the primary hypotheses.

Standard protocol approvals, registrations, and patient consents. This trial was approved by institutional review boards at each institution and all participants were consented accordingly. A Data Safety Monitoring Board monitored the conduct of the study and safety of participants. The trial was registered with ClinicalTrials.gov, number NCT00147446.

Randomization. An independent statistician, blind to initial assessment to ensure allocation concealment, used computer generated randomization with a 1:1 ratio, stratified by site, and block size of 4 within each site. Treatment assignment was communicated to the patient by the central study coordinator to prevent unblinding of local evaluators.

Participant inclusion criteria. Eligible participants were diagnosed with MS according to the MacDonald criteria[8] and had documented evidence of clinical exacerbation or at least 1 Gd+ MRI brain lesion within 12 months prior to enrollment. The qualifying exacerbation or Gd+ lesion had to have occurred at least 1 month after initiation of an interferon drug or 6 months after initiation of glatiramer acetate. All participants were at least 18 years of age, were able to speak and read English, and had a score of 0–6.5 on the Expanded Disability Status Scale (EDSS).[9] Participants were excluded if they had received corticosteroids in the past 28 days, were treated with a cytotoxic agent or natalizumab, had other autoimmune or endocrine disorders, were unable to undergo Gd+ MRI, were pregnant or planning pregnancy, were diagnosed using the Mini International Neuropsychiatric Interview[10] with any severe psychiatric disorder (e.g., psychotic disorders, bipolar disorder), or were currently receiving or planning to begin psychotherapy. Participants were also excluded if they met criteria for dementia, defined consistent with previous trials[11] as being below the fifth percentile on 3 or more of the following: Symbol Digit Modalities, Digit Span, Hopkins Verbal Learning Test, Controlled Word Association Test, Similarities, and the 10/36 test.

Treatment. Eligible participants were randomized to receive either the active treatment, SMT-MS, or a wait-list control condition in addition to their current disease-modifying therapy (DMT) regimen.

SMT-MS is a manualized, validated, published stress management program designed for patients with MS.[5,7] Participants met with a therapist for 16 individual 50-minute sessions conducted over 20–24 weeks. The first 6 sessions focused on teaching problem solving skills, relaxation, increasing positive activities, cognitive restructuring, and enhancement of social support. Participants were able to tailor the treatment to meet their needs using optional treatment modules including communication and assertiveness training, fatigue management, anxiety reduction, pain management, management of cognitive problems, insomnia treatment, and management of sexual dysfunction. To avoid potential confounds with pharmacologic interventions, therapists were prohibited from discussing the DMTs or psychotropic medications and instructed to refer participants back to the prescribing physician if patients had questions regarding their treatments.

Therapists were 7 PhD level licensed psychologists with more than 3 years postdoctoral experience and 1 licensed social worker who had more than 30 years experience with cognitive behavioral therapy. Treating therapists received 1 day of training in the treatment model and weekly supervision for the first year, which could be reduced to once every 2–3 weeks thereafter, as determined by the supervising psychologists. The supervision team included 3 senior psychologists, including the first author. All sessions were audiotaped. Audiotapes were randomly selected and rated by a supervising psychologist using the Cognitive Therapy Scale[12] to ensure treatment fidelity and for supervision.

Wait list control provided treatment as usual for the first 10+ months of participation. A 5-hour workshop was provided after the 10th month. This allowed at least 2 post-treatment MRI evaluations that were not contaminated by the workshop.

Assessment. ***Masking.*** All clinical evaluators and technicians were blinded to treatment assignment.

MRI scanning and analysis. MRI of the brain (T2/T1-weighted images) with injection of a single dose of Gd was performed according to a standardized protocol using a 3.0-Tesla magnet at each site. MRI was performed during baseline and at weeks 8, 16, 24 32, 40, and 48. "Dummy" scans and quality control were performed at each site prior to first subject enrollment. A central MRI reading unit (UCSF, San Francisco) evaluated MRI scans for quality and measurement of the study endpoints according to standardized postprocessing protocols.

The primary outcome was the cumulative number of Gd+ lesions during the active treatment period (weeks 8, 16, and 24). Secondary outcomes included cumulative number of new and enlarging T2 lesions, number of participants free of Gd+ and of new T2 lesions, percent brain volume change over 48 weeks from volumetric high-resolution (1 mm^3, 124 slices) T1-weighted gradient-echo images using *SIENA*,[13] and change in T2 volume from baseline to week 48. T2 lesion volume analysis was performed on all scans using a semiautomated thresholding method and manual editing with simultaneous view access to both T2 and proton density–weighted slices. An automated coregistration procedure was applied on subsequent time points onto each subject baseline scan.

Stress outcomes. The occurrence of negative stressful events was measured using the Life Events Scale (LES),[14] administered monthly by telephone interview. Assessment of subjective perceived stress was measured by monthly self-report using the Brief Inventory of Perceived Stress (BIPS).[15]

Clinical neurology outcomes. Exacerbations were verified by an evaluating MS physician or trained registered nurse using the same definition implemented in recent DMT trials.[16] Participants were also evaluated clinically at 16-week intervals to document their EDSS and adverse events. Patients with confirmed exacerbations were referred to their physicians for treatment.

Statistical analyses. The power analysis as originally proposed was based on preliminary data derived from monthly MRI scans.[2] Planning for 6 monthly scans during the treatment period, we expected 50% of control participants to have Gd+ lesions on the first scan, dropping to 40% by 24 weeks. Using an intent-to-treat (ITT) analysis, α of 0.05, power of 0.80, 2-tailed testing, and a 10% reduction in the occurrence of Gd+ lesions in the treated arm compared to the control group, we required 60 participants in each group for a total sample size of approximately 120 participants. Funding cuts and other feasibility constraints led to design changes that included reducing the number of scans to every other month. Consequently, using a Wilcoxon test to detect differences in cumulative lesion counts during the treatment period, taking into account missing values, the current study had 59% power to detect a significant difference in cumulative Gd+ lesions.

Data were analyzed using SAS (v. 9.2 SAS Corporation, Cary, NC). Demographics and clinical characteristics at baseline between treatment groups were compared using *t* test for continuous data and χ^2 for categorical variables.

The ITT sample included all participants who were randomized. To calculate the primary endpoint it was necessary to impute missing Gd+ lesions at each timepoint. Since new and enlarging T2 lesions were measured since the previous MRI, it was only necessary to impute missing T2 lesions for missing values at week 24. Nonparametric multiple imputation methods were used to impute missing lesion values.[17] Twenty imputations were made for each missing value.

Because small numbers of patients can have unusually large numbers of lesions, nonparametrics are typically used to avoid the influence of outliers. Cumulative lesion counts for both Gd+ and T2 lesions were compared between treatment groups using a Wilcoxon test on each imputed dataset. Test results across the imputed datasets were combined using multiple imputation combining rules described by Li et al.[18] Analyses were conducted during the treatment phase and post-treatment follow-up. Between-group comparisons of the proportion of patients free of lesions were performed using logistic regression, with test statistics combined across the imputed datasets.[18]

Mixed-effects repeated measures model with random subject-specific intercepts was used to detect treatment and time × treatment effects on both LES and BIPS. Percent brain volume changes and the rate of confirmed exacerbation were compared between treatment groups using *t* test and χ^2, respectively. The same method of comparing cumulative lesions counts was used to check the relationship between MRI lesion activity and DMT.

RESULTS

Study participants. Recruitment occurred from May 2005 through January 2008, and follow-up evaluations were completed in January 2009. The baseline characteristics of the participants are displayed by treatment group in table 1. There was a trend toward the SMT-MS group having a higher EDSS than the control condition ($p = 0.06$), although this difference was clinically not meaningful. There were no significant differences across treatment groups in any other demographic or disease variables ($ps > 0.24$).

Treatment adherence. Of the 60 participants assigned to SMT-MS, 50 (83.3%) were classified as treatment completers (12 or more sessions).

Lost to follow-up. A CONSORT diagram showing the flow of participants through each stage of this randomized controlled trial is displayed in figure 1. The lost to follow-up rate was not significantly different across treatment arms ($\chi^2 = 3.20$, $p = 0.07$). The lost to follow-up rate was not significantly related to any baseline demographic or clinical variables (all $ps > 0.31$).

Primary endpoint and secondary MRI outcomes: Treatment period. Treatment with SMT-MS produced a significant reduction in cumulative Gd+ lesions compared to the control condition during the treatment period (table 2; $p = 0.04$). The median (value at the 50th percentile) number of new Gd+ lesions was 0 in both groups, given most participants had no new Gd+ lesions during the 24-week treatment period, but the difference was apparent at the upper end of the distributions. Using the upper 75th percentile, participants in SMT-MS had 0 lesions, compared with 1 lesion in the control condition. As shown in figure 2, significantly greater numbers of participants receiving SMT-MS remained free of Gd+ lesions during the treatment, compared to those receiving the control condition (76.8% vs 54.7%, OR = 2.77; 95% CI = 1.17–6.55; $p = 0.02$). The absolute risk reduction was 22.2% and the number needed to treat (NNT) = 5.

Participants receiving SMT-MS showed a significant reduction in cumulative new T2 lesions, compared to those receiving the control condition (median = 1 vs 0; 75th percentile = 3 vs 1; $p = 0.005$). Similarly, figure 2 shows that significantly greater numbers of participants receiving SMT-MS remained free of new T2 lesions, compared to control condition participants (69.5% vs 42.7%, OR = 3.07; 95% CI = 1.38–6.81; $p = 0.006$). As T2 imaging is more sensitive than Gd+ to events over an 8-week interval, figure 3 also displays the percentage of patients free of T2 lesions at each time point throughout the entire study. The absolute risk reduction was 26.8% and NNT = 4.

MRI outcomes: Post-treatment. There were no statistically significant differences across treatment arms in cumulative Gd+ lesions or new T2 lesions on any analyses during the post-treatment follow-up weeks 32–48 ($ps > 0.45$). The difference in the number of participants remaining free of Gd+ lesions during

Table 1 Demographics and baseline disease characteristics

	SMT-MS (n = 60)	WLC (n = 61)	Total patients (n = 121)	p Value
Demographics, n (%)				
Female	51 (85)	50 (82)	101 (83)	0.65
Caucasian	49 (82)	51 (84)	100 (83)	0.78
Age, y				0.72
Mean (SD)	42.33 (9.03)	42.98 (10.56)	42.66 (9.79)	
Median (range)	41.50 (27–59)	41.00 (24–69)	41.00 (24–69)	
Years since MS diagnosis				0.06
Mean (SD)	5.68 (5.13)	8.42 (9.05)	7.05 (7.45)	
Median (range)	5.00 (0.08–23)	5.00 (0.08–51)	5.00 (0.08–51)	
MS disease status, n (%)				0.24
Relapsing-remitting	57 (97)	61 (100)	118 (98)	
Secondary progressive	2 (3)	0 (0)	2 (2)	
Psychiatric diagnoses, n (%)				
Major depressive disorder	9 (15.0)	7 (11.5)	16 (13.2)	0.57
Dysthymic disorder	4 (6.7)	4 (6.6)	8 (6.6)	0.99
Generalized anxiety disorder	9 (15.0)	13 (21.3)	22 (18.2)	0.37
Other anxiety disorders	12 (20)	13 (21.3)	25 (20.7)	0.86
MS medication, n (%)				0.96
Interferon-β 1a (Avonex) 100	8 (14)	10 (16)	18 (15)	
Interferon-β 1b (Betaseron) 101	5 (9)	5 (8)	10 (9)	
Interferon-β 1a (Rebif) 108	25 (44)	23 (38)	48 (41)	
Glatiramer acetate 103	8 (14)	9 (15)	17 (14)	
None	11 (19)	14 (23)	25 (21)	
Expanded Disability Status Scale score				0.06
Mean (SD)	3.36 (1.48)	2.84 (1.54)	3.10 (1.52)	
Median (range)	3.50 (0–6)	3.00 (0–6)	3.50 (0–6)	
Gd+ lesions at baseline, n (%)				0.33
0	48 (80)	49 (80)		
1–2	9 (15)	12 (20)		
3–5	3 (2)	0 (0)		
>5	2 (3)	0 (0)		
Total	43	17	60	
Mean (SD)	0.72 (3.31)	0.28 (0.61)	0.50 (2.37)	
Median (range)	0.00 (0–25)	0.00 (0–2)	0.00 (0–25)	

Abbreviations: MS = multiple sclerosis; SMT-MS = stress management therapy for multiple sclerosis; WLC = wait list control.

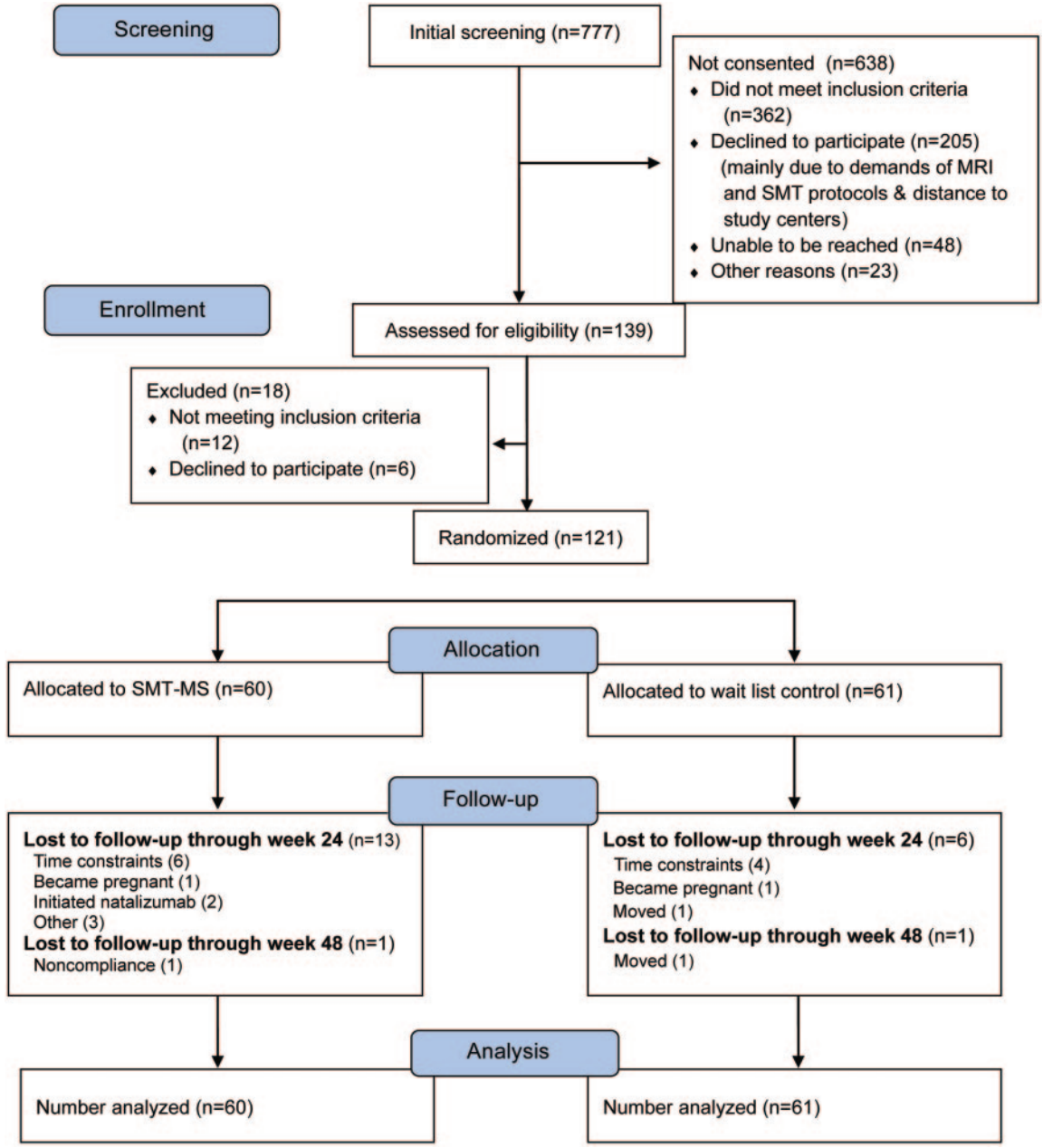
the post-treatment follow-up remained marginally significant (60.6% vs 43.0%, $p = 0.08$), but there was no significant effect for remaining free of T2 lesions through week 48 ($p = 0.11$).

Change in T2 lesion volume and atrophy. Because one would not expect to see changes in T2 lesion volume or atrophy over periods less than 48 weeks, these were examined over the entire study period. There was no significant difference in change in T2 lesion volume across treatment arms ($p = 0.37$). However, there was significantly less percent brain volume change among participants receiving SMT-MS (mean loss −0.11%) compared to those receiving the control condition (mean loss −0.43%; $p = 0.01$).

MRI outcomes and DMT. The effect of SMT-MS on Gd+ and new T2 lesion counts did not vary by DMT status ($ps > 0.20$).

Stress outcomes. Participants receiving SMT-MS showed significantly reduced levels of stress from baseline to week 24 on the LES (SMT-MS baseline = 3.1 ± 2.3, post-treatment = 1.5 ± 1.2; con-

Figure 1 Participant flow chart



SMT-MS = stress management therapy for multiple sclerosis.

trol baseline = 2.9 ± 2.3, post-treatment = 1.8 ± 1.2; $p = 0.04$) and the total BIPS (SMT-MS baseline = 18.2 ± 5.7, post-treatment = 16.3 ± 6.2; control baseline = 17.3 ± 6.3, post-treatment = 17.5 ± 6.2; $p = 0.0007$). There was no treatment effect for either the LES ($p = 0.34$) or the BIPS during weeks 32–48 ($p = 0.18$).

Clinical neurology outcomes. There were no significant differences in the number of confirmed exacerbations, either from baseline to week 24 (22 in both arms; $p = 0.84$) or from week 24 through week 48 (15 in SMT vs 18 in control; $p = 0.40$). Similarly, there were no differences in EDSS over the trial period ($p = 0.15$).

Adverse events. There were no serious adverse events associated with SMT-MS.

DISCUSSION This RCT found significantly fewer new Gd+ brain lesions and new or enlarging T2 lesions among participants treated with SMT-MS, compared to the control group, indicating that SMT-MS can reduce not only the extent of blood–brain barrier opening, but also the accumulation of fixed lesions. These outcomes were not influenced by

Table 2 MRI endpoints

	WLC (n = 61), n (%)	SMT-MS (n = 60), n (%)
No. of Gd+ lesions (to week 24)		
0	33 (55)	46 (77)
1	13 (21)	5 (8)
2	6 (10)	2 (3)
3	6 (10)	2 (4)
≥4	3 (5)	5 (8)
No. of Gd+ lesions (weeks 32–48)		
0	37 (61)	41 (69)
1	11 (18)	7 (12)
2	2 (3)	3 (5)
3	2 (4)	4 (6)
≥4	9 (14)	5 (8)
No. of new or enlarging T2 lesions (to week 24)		
0	26 (43)	43 (71)
1	9 (15)	8 (14)
2	9 (14)	1 (2)
3	7 (11)	1 (2)
≥4	10 (16)	7 (12)
No. of new or enlarging T2 lesions (weeks 32–48)		
0	36 (59)	38 (63)
1	10 (17)	6 (10)
2	1 (1)	4 (6)
3	3 (4)	4 (6)
≥4	12 (19)	9 (15)

Abbreviations: Gd+ = gadolinium-enhancing; SMT-MS = stress management therapy for multiple sclerosis; WLC = wait list control.

DMT status, and were achieved with no adverse side effects. The effect sizes were similar to other recent phase II trials of new pharmacotherapies.[19]

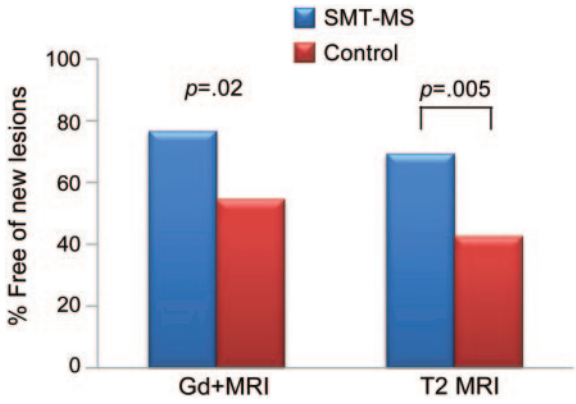
These findings are consistent with epidemiologic studies showing that stressful life events increase the risk of new Gd+ MRI lesions[2] and MS exacerbations[20] and provide more conclusive evidence of the link between stress and MRI activity, given that the RCT design eliminates potential biases that are inherent in epidemiologic studies. Our results are especially encouraging since we selected our participants for higher disease activity.

The differences in outcomes between treatment groups during the treatment period were not sustained during the post-treatment follow-up period. The effect on atrophy over 48 weeks, while worthy of further investigation, was unexpected and therefore cannot be interpreted. There are at least 2 possible explanations why neuroimaging outcomes were not maintained. It is possible that participants learned and implemented new coping skills during the trial, but were unable to sustain these new behaviors once the support of active treatment ended. Difficulty maintaining behavior change after treatment cessation is a problem encountered by many behavioral interventions[21] and can also occur among patients with MS.[22] Alternatively, it may be that nonspecific treatment factors such as patient expectancies or the experience of a supportive relationship were responsible for the changes in Gd+ lesions. Both of these have been shown to affect immune function.[23,24] In either case, these data suggest that maintaining the effects over longer periods of time may require more sustained intervention. However, long-term standard behavioral intervention can be burdensome for patients who must make weekly office visits. More accessible models of providing care using telecommunications media may make sustained interventions accessible to patients. Indeed, SMT-MS has been shown to be effective when delivered via telephone[25] and a growing literature indicates that Internet and smartphone interventions can be effective.[26]

A number of the hypothesized pathways have been described by which stress or SMT-MS may affect MS disease activity,[27,28] most notably via the number and function of glucocorticoid receptors on immune cells. Future analyses of data from this trial will examine secondary hypotheses regarding such biological and psychosocial pathways. Understanding these pathways may allow refinements to the intervention that can more specifically target factors affecting MS pathogenic processes.

There are limitations in our study that should be considered. First, this trial was not powered to detect clinical outcomes, and indeed, there was no evidence that SMT-MS reduced clinical outcomes. Second, while differences in the lost to follow-up rate did not differ significantly across treatment arms, they did differ marginally. The lost to follow-up rate of 22% in SMT-MS is comparable to many other trials of behavioral interventions,[29] while the loss of 10% of participants in the wait list control condition is consistent with rates seen in pharmaceutical trials in MS trials more generally.[16,30] There was no evidence that dropout was related to demographic or disease-related variables and our statistical analyses attempted to control for the lost to follow-up using imputation. However, it is possible that there were other unmeasured variables that that could have introduced bias. While the 22% attrition rate is not unexpected, delivering care via telephone or other media (videoconferencing, Internet) can improve adherence with similar levels of efficacy.[31]

Figure 2 Percent of participants free of gadolinium-enhancing (Gd+) and T2 lesions by treatment group during 24-week treatment period

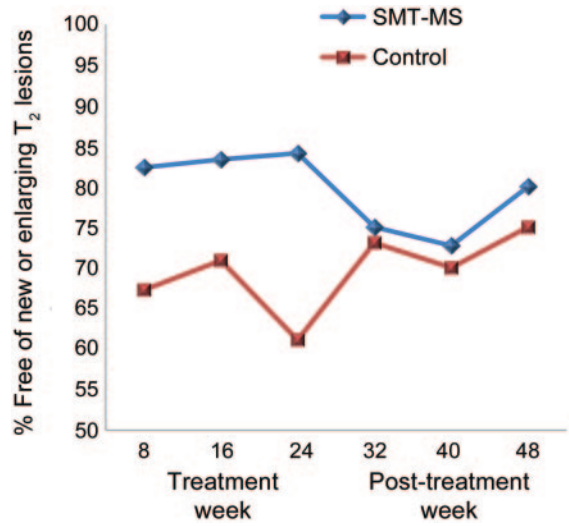


SMT-MS = stress management therapy for multiple sclerosis.

Finally, the wait list control did not control for nonspecific factors such as attention. An examination of the mediating factors in SMT-MS that contribute to the outcomes is planned for a separate publication.

While SMT-MS has repeatedly been demonstrated to produce many benefits, including improved mood, fatigue, and quality of life among people with MS,[25,32–34] we caution that it is premature to make specific clinical recommendations regarding the use of SMT-MS to manage MS disease-related activity. Future work should identify, refine, and optimize the active ingredients in this behavioral intervention. Clinical outcomes will be important to assess in the future in phase III trials.

Figure 3 Percentage of participants free of new or enlarging T2 lesions at each time point by treatment group



SMT-MS = stress management therapy for multiple sclerosis.

AUTHOR CONTRIBUTIONS

David C. Mohr, PhD: principal investigator, conceptualization of the trial, oversaw all aspects of the conduct of the trial, interpreted data, wrote much of the paper. Jesus Lovera, MD: conducted much of the analysis of the MRI data, including identification of Gd+ lesions. Ted Brown, MD: site PI for Seattle, contributed to conduct of the study, interpretation of data, and writing of paper. Bruce Cohen, MD: site investigator for Northwestern: contributed to conduct of study, interpretation of data, and writing of paper. Thomas Neylan, MD: coinvestigator, contributed to conceptualization of trial, interpretation of data, writing of paper. Roland Henry, PhD: coinvestigator; is an MRI physicist who defined MRI protocols and the analysis of MRI data. Juned Siddique, DrPH: coinvestigator and statistician; designed statistical analytic plan and oversaw analyses. Ling Jin, MS: conducted statistical analyses, wrote sections of the paper. David Daikh, MD: coinvestigator who assisted in the conceptualization of the study and writing of the paper. Daniel Pelletier, MD: coinvestigator who assisted in the conceptualization of the study, oversaw neurological examinations, analysis of MRI data, assisted in the interpretation of data and writing of the paper.

ACKNOWLEDGMENT

The authors thank the following team members for their contributions: Claudine Catledge, MA; Cynthia Lotane; Joyce Ho, PhD; Emily Gagen; Mary Carns, MA; Alan Evangelista; Robert Fraser, PhD; Don Brenneman; Monica Bristow, PhD; Stephen Scholl, PhD; Paula Young, PhD; Jenna Duffecy, PhD; Julie Leader, PhD; Kate Gapinski, PhD; Robert Fraser, PhD; Peter Kane, PhD; Paul Malkin, LCSW; Stacey Hart, PhD. The centralized MRI reading was performed by the Advanced Imaging in Multiple Sclerosis (AIMS) Laboratory at UCSF (Dr. Daniel Pelletier, Director). David C. Mohr, PhD, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURE

D. Mohr receives research funding from the NIH. J. Lovera has honoraria for consulting and speaking from Biogen Idec, Serono, and Teva. T. Brown has served as a consultant for Acorda, Biogen, EMD Serono, and Teva Neuroscience and has received honoraria from Acorda, Pfizer, and Teva and has been funded by research grants from Lilly Inc., Acorda, and Teva Neuroscience. B. Cohen has received payments for consulting or speaking honoraria from Accorda, Astellis, Bayer, Biogen-Idec, EMD Serono, Genentech, Novartis, Pfizer, and Teva Neuroscience. He has received research support through Northwestern University from Biogen-Idec, EMD Serono, Novartis, Roche, and an Unrestricted Educational Grant in support of a CME program (through Northwestern University) from Teva Neuroscience. T. Neylan has received research support (supply of investigative medication) from Actelion and Glaxo Smith Kline. R. Henry, J. Siddique, L. Jin, and D. Daikh report no disclosures. D. Pelletier receives research support from the National Institutes of Health, NINDS (R01NS062885). **Go to Neurology.org for full disclosures.**

Received August 11, 2011. Accepted in final form January 17, 2012.

REFERENCES

1. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. BMJ 2004;328:731.
2. Mohr DC, Goodkin DE, Bacchetti P, et al. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. Neurology 2000;55:55–61.
3. Mohr DC, Goodkin DE, Nelson S, Cox D, Weiner M. Moderating effects of coping on the relationship between stress and the development of new brain lesions in multiple sclerosis. Psychosom Med 2002;64:803–809.

4. Somer E, Golan D, Dishon S, Cuzin-Disegni L, Lavi I, Miller A. Patients with multiple sclerosis in a war zone: coping strategies associated with reduced risk for relapse. Mult Scler 2010;16:463–471.
5. Mohr DC. The Stress and Mood Management Program for Individuals With Multiple Sclerosis: Workbook. New York: Oxford Press; 2010.
6. Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. Ann Neurol 2009;65:268–275.
7. Mohr DC. The Stress and Mood Management Program for Individuals With Multiple Sclerosis: Therapist Guide. New York: Oxford Press; 2010.
8. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840–846.
9. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
10. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33.
11. Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. J Consult Clin Psychol 2001;69:942–949.
12. Vallis TM, Shaw BF, Dobson KS. The cognitive therapy scale: psychometric properties. J Consult Clin Psychol 1986;54:381–385.
13. Smith SM, De Stefano N, Jenkinson M, Matthews PM. Normalized accurate measurement of longitudinal brain change. J Comput Assist Tomogr 2001;25:466–475.
14. Cohen S, Tyrrell DAJ, Smith AP. Psychological stress and susceptibility to the common cold. N Engl J Med 1991; 325:606–612.
15. Lehman KA, Burns MN, Gagen E, Mohr DC. Development of the Brief Inventory of Perceived Stress. J Clin Psychol 2012;68:631–644.
16. Togha M, Karvigh SA, Nabavi M, et al. Simvastatin treatment in patients with relapsing-remitting multiple sclerosis receiving interferon beta 1a: a double-blind randomized controlled trial. Mult Scler 2010;16:848–854.
17. Siddique J, Belin TR. Multiple imputation using an iterative hot-deck with distance-based donor selection. Stat Med 2008;27:83–102.
18. Li KH, Raghunathan TE, Rubin DB. Large sample significance levels from multiply-imputed data using moment-based statistics and an F reference distribution. J Am Stat Assoc 1991;86:1065–1073.
19. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008; 372:1463–1472.
20. Mohr DC. The relationship between stressful life events and inflammation in patients with multiple sclerosis. In: Welsh CJ, Meagher M, Sternberg E, ed. Neural and Neuroendocrine Mechanisms in Host Defense and Autoimmunity. New York: Kluwer Academic/Plenum Publishers; 2006:255–267.
21. Nilsen WJ, Haverkos L, Nebeling L, Taylor MV. Maintenance of long-term behavior change. Am J Health Behav 2010;34:643–645.
22. Mohr DC, Epstein L, Luks TL, et al. Brain lesion volume and neuropsychological function predict efficacy of treatment for depression in multiple sclerosis. J Consult Clin Psychol 2003;71:1017–1024.
23. Segerstrom SC, Sephton SE. Optimistic expectancies and cell-mediated immunity: the role of positive affect. Psychol Sci 2010;21:448–455.
24. Mohr DC, Genain C. Social support as a buffer in the relationship between treatment for depression and T-cell production of interferon gamma in patients with multiple sclerosis. J Psychosom Res 2004;57:155–158.
25. Mohr DC, Hart SL, Julian L, et al. Telephone-administered psychotherapy for depression. Arch Gen Psychiatry 2005;62: 1007–1014.
26. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. Cogn Behav Ther 2009;38:196–205.
27. Mohr DC, Pelletier D. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. Brain Behav Immun 2006;20:27–36.
28. Gold S, Mohr DC, Huitinga I, Schulz KH, Heesen C. The role of stress response systems in the pathogenesis and progression of multiple sclerosis. Trends Immunol 2005;26: 644–652.
29. Wierzbicki M, Pekarik G. A meta-analysis of psychotherapy dropout. Prof Psychol Res Pract 1993;24:190–195.
30. Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol 2010;9: 381–390.
31. Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: a meta-analysis. Clin Psychol Sci Pract 2008;15:243–253.
32. Mohr DC, Likosky W, Bertagnolli A, et al. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. J Consult Clin Psychol 2000;68:356–361.
33. Mohr DC, Hart S, Vella L. Reduction in disability in a randomized controlled trial of telephone-administered cognitive-behavioral therapy. Health Psychol 2007;26: 554–563.
34. Grossman P, Kappos L, Gensicke H, et al. MS quality of life, depression, and fatigue improve after mindfulness training: a randomized trial. Neurology 2010;75:1141–1149.