Association Between Pain and Mindfulness in Multiple Sclerosis

A Cross-sectional Survey

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Background: ***Chronic pain is a common symptom in people with multiple sclerosis (MS) and often requires a multimodal approach to care. The practice of mindfulness has been shown to decrease the experience of pain in other conditions, yet little is known about the relationship between mindfulness and pain in people with MS. The objective of this study was to evaluate the association between pain interference and trait mindfulness in people with MS.***

Methods: ***In this cross-sectional survey, 132 people with any type of MS completed the Patient-Reported Outcomes Measurement Information System Pain Interference scale and the Five Facet Mindfulness Questionnaire. Linear regression was used to test the association between pain and mindfulness while adjusting for demographic and MS-related characteristics.***

Results: ***The relationship between pain and mindfulness was clinically meaningful and highly significant ($t = -5.52$, $P < .0001$). For every 18-point increase in mindfulness scores, pain interference scores are expected to decrease by 3.96 (95% CI, –2.52 to –5.40) points ($\beta = -0.22$, $P < .0001$). The adjusted model, including age, type of MS, the interaction between mindfulness and age, and the interaction between mindfulness and MS type, explains 26% of the variability in pain interference scores ($R^2 = 0.26$).***

Conclusions: ***These results suggest a clinically significant association between mindfulness and pain interference in MS and support further exploration of mindfulness-based interventions in the management of MS-related pain.*** ***Int J MS Care*. 2018;20:28-34.**

Up to 80% of people with multiple sclerosis (MS) experience pain,[1,2] and up to one-third report that pain is either a significant or the most significant symptom of their disease.[3,4] Pain often interferes with activities of daily living and sleep, compromising occupational and social roles for many.[5,6] People experience various types of pain, including central neuropathic pain (eg, dysesthetic extremity pain, tonic muscle spasm, or trigeminal neuralgia), musculoskeletal pain (such as low back pain), or mixed neuropathic and nonneuropathic forms of pain (eg, headaches).[2] There are limited pharmacological trial data for managing MS-related pain, and many treatment plans are derived from evidence of effect in similar conditions and clinical experience.[7,8] In addition to treating pain directly, the effect of pain on mood, sleep, mobility, and social roles often needs to be addressed with a multimodal approach to care.[9] A recent survey by Ehde et al.[10] found that people with MS used an average of nine methods to manage their pain, medications being the most frequently tried approach, with few treatments providing even moderate relief. Many people with MS report dissatisfaction with their pain management plans,[6,10] and there is a compelling need to identify effective interventions that reduce the experience of pain.

Mindfulness is the ability to be wholly present with one's experience.[11] Jon Kabat-Zinn first studied the practice of mindfulness as a behavioral intervention for pain in 1982[12] and describes mindfulness as "paying attention in a particular way; on purpose, in the present

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moment, and non-judgmentally."[13(p4)] Observing without judgment is a distinguishing feature of mindfulness, and this includes one's experience of pain. In mindfulness practice, there is an attempt to let go of defense, resistance, or protection against pain and a movement toward acceptance.[12] Mindfulness-based intervention studies have found positive effects for chronic pain in fibromyalgia, low back pain, arthritis, and a variety of somatization disorders,[14-18] but very few trials have been conducted in MS. Three small mindfulness-based MS trials have demonstrated significant trends toward pain reduction, yet results are difficult to interpret due to limitations in sample size and study design.[19-21] To explore the appropriateness of future mindfulness-based interventions targeting pain in MS, we evaluated the relationship between pain interference and trait mindfulness in 132 people with MS.

Methods

Overview and Study Participants

The methods for this cross-sectional survey have been previously described.[22] After approval was received from the Oregon Health & Science University institutional review board, a convenience sample of men and women was recruited during outpatient visits to the MS Center at the university and through MS community events. Participants completed several questionnaires during one study visit. The inclusion criteria comprised any type of MS, the ability to read and write in English, and age 18 to 90 years. The exclusion criteria included a relapse or exacerbation in the previous 90 days. The MS diagnosis was confirmed by medical record review according to the 2010 McDonald criteria.[23] Any questions regarding a participant's diagnosis were discussed with their neurologist. From December 1, 2011, through February 28, 2013, 150 people with MS were recruited, gave written consent, and partook in the study.

Dependent Variable

Pain interference is a subjective measure of how much pain limits one's ability to engage in daily and recreational activities. Pain interference, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain–Interference computerized adaptive test (National Institutes of Health [NIH], Bethesda, MD), was the dependent variable in all the analyses. Scores are reported on a T-score metric with a mean ± standard deviation (SD) of 50 ± 10, referenced to the mean for the general US population.[24] Thus, a score of 60 on PROMIS Pain–Interference is 1 SD above the mean of a normative US sample. Higher scores indicate increased pain interference. When administered to people with MS, PROMIS Pain–Interference is highly correlated with the Medical Outcomes Study Pain Effects Scale (a validated subscale of the Multiple Sclerosis Quality of Life Inventory[25]; $r = 0.86$) and demonstrates strong convergent and discriminatory validity compared with the Pain Effects Scale.[26] PROMIS Pain–Interference shows no evidence of differential item functioning between people with MS and those with other disabling conditions (spinal cord injury, muscular dystrophy, postpolio syndrome) or across age groups within MS.[27]

Independent Variables

Trait mindfulness was the primary predictor variable for these analyses and was measured by the total score on the Five Facet Mindfulness Questionnaire (FFMQ).[28] The FFMQ is a 39-item, Likert-type questionnaire that measures five elements of trait mindfulness: observing, describing, acting with awareness, nonjudgment, and nonreactivity, providing a total score and five subscale scores. The overall FFMQ score ranges from 39 to 195, with higher scores indicating higher levels of mindfulness. The subscales show adequate-to-good internal consistency, with the coefficient alpha ranging from 0.72 to 0.92,[28] and are sensitive to change in participants of mindfulness-based interventions.[29] The FFMQ has not yet been validated for specific use with people with MS.

Six demographic characteristics that might affect the relationship between pain and mindfulness were assessed for potential interaction and confounding: age (continuous variable), MS disease-modifying therapy (DMT) use (categorical; yes or no), education (categorical; some college or less vs. bachelor's degree or higher), MS type (categorical; relapsing-remitting, secondary progressive, or primary progressive), sex (categorical; male or female), and self-reported level of disability (continuous; 6-point scale). The disability scale asked participants to identify which of six statements best described their MS; statements ranged from "I have no or minimal MS-related symptoms, no limitations in my walking ability, and no limitations in daily activities" to "I have many severe MS-related symptoms and am restricted to a wheelchair or bed." This scale is a modified version of the Patient-Determined Disease Steps scale[30] and has previously been shown to correlate with the Expanded Disability

Status Scale, a clinician-rated, objective measure of disease severity (r = 0.85).[31]

Statistical Analysis

Exploratory analysis was conducted to ensure that assumptions of linearity and normality were met. Pairwise correlations were used to explore preliminary relationships between all the variables. Continuous variables are described as mean ± SD and categorical variables as frequency (percentage). Linear regression was used to test the association between pain and mindfulness. A P value < .05 was considered statistically significant for the association between pain and mindfulness. All the independent variables described herein were assessed for interaction with the primary predictor (mindfulness). If including a covariate and its interaction with mindfulness yielded $P \leq .10$ for the interaction term, then the covariate and the interaction term were retained in the model. Independent variables that demonstrated no interaction with the primary predictor were further assessed for potential confounding. Any variable that changed the unstandardized regression coefficient for the effect of mindfulness on pain by more than 10% (relative to the simple model) was retained as a covariate in the full model. Diagnostic tests to assess normality, linearity, homoscedasticity, collinearity, and the influence of outliers were conducted for all the models. Collinear terms were centralized for any model with a mean variance inflation factor greater than 10. All the analyses were performed using Stata for Mac, version 14 (StataCorp LLC, College Station, TX).

Results

Sample Size and Participant Characteristics

Two hundred fourteen people with MS were assessed for study eligibility (Figure 1). Sixty-four people declined to participate or did not meet the inclusion criteria; 150 people participated in the study visit. Four participants were dropped from the analysis: MS diagnosis could not be verified (n = 3) and relapse within the past 90 days (n = 1). Fourteen participants were unable to complete the entire study visit due to survey fatigue, and because the PROMIS Pain–Interference questionnaire was administered at the end of the visit; these 14 participants are missing the necessary data for inclusion in the present analysis. Missing (n = 14) and excluded (n = 4) data resulted in a final sample size of 132 for this analysis.

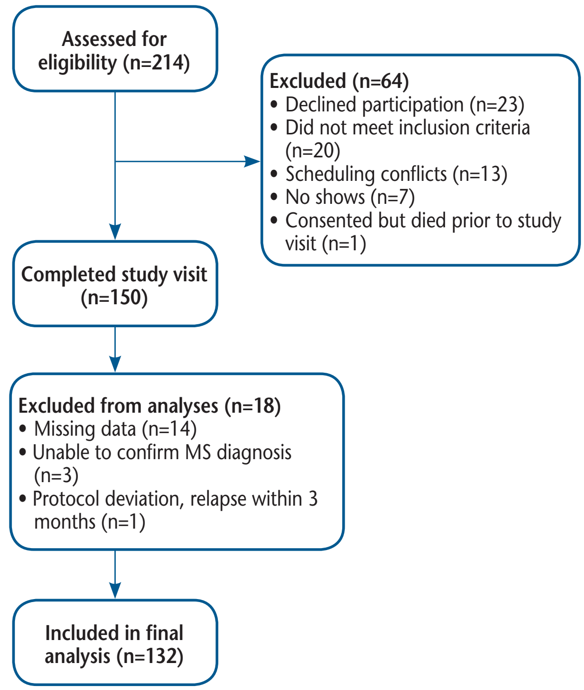

***Figure 1.* Study flow diagram**

MS, multiple sclerosis.

Demographic and clinical characteristics of the study sample are shown in Table 1. Most participants were women (78%), and the mean ± SD age of the study sample was 50.45 ± 12.85 years. Most participants had relapsing-remitting MS (74%), and 70% of participants were taking some kind of MS DMT, including glatiramer acetate, interferon beta-1b, interferon beta-1a, natalizumab, and fingolimod. Seventy-three percent of the participants experienced minimal-to-moderate disability, 23.5% of participants needed an assistive device to walk, and 3% of participants were restricted to a wheelchair. The mean ± SD total mindfulness score was 132 ± 21.5 (respondent range, 74-182; questionnaire range, 39-195). The mean ± SD pain interference score was 52 ± 9.5 (respondent range, 39-72).

Identification of Potential Covariates, Confounders, and Effect Modifiers

The bivariate Pearson correlation between pain and mindfulness in this sample was r = –0.37 (P < .0001). According to the simple model, for every 18-point increase in the mindfulness score we would expect the Pain–Interference score to decrease by 2.88 points, approximately one-quarter of an SD relative to the general US population (β = –0.16) (Table 2, model A). We chose to look at an 18-point increase in mindfulness

Table 1. Demographic and clinical data (n = 132)

Characteristic	Value
Age, mean ± SD, y	50.45 ± 12.85
Female sex, No. (%)	103 (78)
DMT use, No. (%)[a]	
Yes	92 (70)
No	40 (30)
Education, No. (%)	
High school diploma	50 (38)
College graduate	82 (62)
Type of MS, No. (%)	
Relapsing-remitting	98 (74.3)
Secondary progressive	23 (17.4)
Primary progressive	11 (8.3)
Disability, No. (%)	
None/minimal	27 (20.5)
Mild	38 (28.8)
Moderate	32 (24.2)
Some support needed	24 (18.2)
Walker or two-handed crutch	7 (5.3)
Unable to walk	4 (3.0)
Ethnicity, No. (%)	
White	121 (92)
Other	11 (8)

Abbreviations: DMT, disease-modifying therapy; MS, multiple sclerosis.
[a]DMTs included glatiramer acetate, interferon beta-1b, interferon beta-1a, natalizumab, and fingolimod.

scores because, as subsequently discussed, several studies demonstrate a mean increase in the FFMQ of 18 points after mindfulness training. The six demographic characteristics (age, sex, level of disability, type of MS, DMT use, and education) were individually assessed for interaction with the primary predictor, mindfulness. Both MS type (t = 1.84, P = .07) and age (t = 1.92, P = .06) were considered significant for interaction and were retained as predictors in the final model. The four remaining demographic variables were individually assessed for confounding; none of them changed the slope of the relationship between pain and mindfulness by more than 10%. The final association model included mindfulness, age, type of MS, the interaction between mindfulness and age, and the interaction between mindfulness and type of MS (Table 2, model B). Mindfulness and age were centralized to reduce collinearity, bringing the mean variance inflation factor for the model to 1.64.

Adjusted Effects of Mindfulness on Pain–Interference

In the main analysis, adjusted for age, type of MS, the interaction between mindfulness and age, and the interaction between mindfulness and MS type, the relationship between pain and mindfulness was highly significant (t = –5.52, P < .0001). For every 18-point increase in the mindfulness score, the Pain–Interference score is expected to decrease by 3.96 points (β = –0.227, P < .0001). Overall, the model explains 26% of the variability in Pain–Interference scores (R^2 = 0.26) (Table 2, model B).

Sensitivity Analyses

Because there was a substantial difference in the number of people with relapsing-remitting MS (n = 98), secondary progressive MS (n = 23), and primary progressive MS (n = 11), we conducted two sensitivity analyses of the variable MS type. In the first analysis we collapsed

Table 2. Crude and adjusted linear regression models for primary relationship between pain interference and trait mindfulness

Model	β (95% CI)	t	P value	Adj R^2	R^2	Δ in pain (95% CI)
A: pain vs. mindfulness only	–0.16 (–0.23 to –0.09)	–4.57	<.0001	0.13	0.14	–2.88 (–4.14 to –1.62)
B: pain vs. mindfulness + covariates	–0.22 (–0.30 to –0.14)	–5.52	<.0001	0.22	0.26	–3.96 (–5.40 to –2.52)
Sensitivity analyses						
C: pain vs. mindfulness + covariates, MS type collapsed	–0.17 (–0.25 to –0.08)	–4.01	<.0001	0.21	0.24	–3.06 (–4.50 to –1.44)
D: pain vs. mindfulness + covariates, MS type removed	–0.14 (–0.21 to –0.08)	–4.18	<.0001	0.21	0.22	–2.52 (–3.78 to –1.44)

Note: Table shows standardized coefficient and significance of mindfulness predictor in each model, as well as R^2 and adjusted R^2 for complete model. Far-right column represents expected change in Patient-Reported Outcomes Measurement Information System Pain–Interference scores based on an 18-point increase in total Five Facet Mindfulness Questionnaire scores. Model B covariates include age, MS type (relapsing-remitting, secondary progressive, or primary progressive), interaction between mindfulness and age, and interaction between mindfulness and MS type. Model C covariates include age, MS type (relapsing or progressive), interaction between mindfulness and age, and interaction between mindfulness and MS type, with MS type collapsed from three to two levels. Model D covariates include age and interaction between mindfulness and age, with MS type removed from model.
Abbreviations: Adj, adjusted; MS, multiple sclerosis.

MS type into two levels (relapsing [n = 98] or progressive [n = 34]) and reran the final association model (Table 2, model C). In the second analysis we removed MS type and the interaction between mindfulness and type and reran the final model (Table 2, model D). When MS type is removed from the model altogether, an 18-point increase in the mindfulness score is expected to result in a 2.5-point decrease in the Pain–Interference score ($\beta = -0.14$, $P < .0001$).

Discussion

Several studies have examined determinants of pain in MS,[2,3,6,32] but none have assessed trait mindfulness as a potential predictor of pain interference. These data show a strong and significant association between greater mindfulness and lower levels of pain interference, even after adjusting for age and type of MS. These results echo findings from Schütze et al.,[33] who, in a heterogeneous sample of people with chronic pain, found the correlation between pain interference and trait mindfulness to be $r = -0.30$ ($P = .002$). In a simple regression model, the authors reported that FFMQ scores accounted for approximately 17% of the variability in pain interference scores, a comparable result to that obtained using the present model A (Table 2). The present analyses suggest that up to 26% of the variability in pain interference could be explained by MS type, age, and mindfulness alone. With the need for more effective approaches to manage MS pain, these findings are notable and warrant further exploration.

In the present study, the raw correlation between pain and disability was $r = 0.31$ ($P = .0002$). Some previous studies have reported that MS-related disability is associated with pain,[3,6] whereas others have found no association.[34,35] Possible explanations for conflicting findings include vast differences in sample sizes (with larger, survey studies more likely to find significant associations), different aspects of pain explored (acute pain, chronic pain, experience of any pain, frequency, intensity, or pain interference), different instruments used to measure different aspects of pain, and differences in how MS-related disability is measured (clinical examination or self-report). Thus, the relationship between pain and disability remains unclear. We did not see a significant association between disability and trait mindfulness ($r = -0.012$, $P = .99$), which suggests that interventions intent on building mindfulness skills may enhance trait mindfulness across people with varying degrees of physical abilities.

The primary analysis suggests that with an 18-point increase in the total FFMQ score, one could expect the PROMIS Pain–Interference score to decrease 4 points (95% CI, 2.52- to 5.4-point decrease) (Table 2, model B). The FFMQ is responsive to change, and several trials have demonstrated a mean 18-point increase in total FFMQ scores after mindfulness-based interventions.[29,36,37] Our predictions for change are statistically significant and may likewise be clinically meaningful. Minimally important differences have yet to be determined for people with MS, but, for cancer-related pain, Yost et al.[38] report that minimally important differences for PROMIS Pain–Interference likely range from 4 to 6 points. The 95% CI for our primary model includes clinically meaningful change, yet the interval is fairly wide, and future studies with larger sample sizes are needed to decrease uncertainty.

Very few mindfulness-based interventions have been conducted with people who have MS,[19-21,39,40] and only some of these have assessed the intervention's effect on pain. Three small trials found significant trends toward pain reduction,[19-21] but the results are difficult to interpret. Tavee et al.[20] conducted an 8-week nonrandomized trial of group meditation training (n = 10 people with MS and 12 people with peripheral neuropathy) versus usual care (n = 7 people with MS and 11 people with peripheral neuropathy). Mean bodily pain scores improved for people with MS in the intervention group (n = 10, $P = .03$) and remained the same for the control group; between-group analyses were not conducted. Mills and Allen[19] conducted a 6-week, one-on-one "mindfulness of movement" intervention using key components of tai chi and qigong (n = 8) compared with usual care (n = 8). The intervention involved "developing a moment to moment awareness of quality of breathing, posture, and movement. Awareness is developed as to whether breathing is shallow or deep, whether posture is aligned or misaligned, and whether movements are integrated with mental preparation or whether there is a sense of mind–body disconnection."[19(p425)] Pain was not assessed using a traditional validated measure. Instead, participants completed a 21-symptom questionnaire indicating whether they felt there was improvement or deterioration of symptoms, including pain, on a 5-point scale. Descriptive data seem to indicate that pain improved in the intervention group compared with the control group; however, statistical analysis was conducted for the entire questionnaire only and not for individual symptoms. Both studies had high dropout rates, and intention-to-treat analyses were not conducted. Bogosian et al.[21] recently provided online mindfulness training to people with progressive MS, in which mindful-movement components were specifically removed from the program. Participants were randomized to receive the intervention (n = 19) or to a wait list control (n = 21). Pain was assessed using a numerical rating scale from 0 to 10 addressing the average intensity of pain associated with MS. No difference in pain intensity was found immediately after the intervention; however, those who received mindfulness training reported significantly less pain intensity compared with controls 3 months after the intervention.

As interest in mindfulness-based interventions continues to grow, it would be useful for future trials to consistently measure pain, pain interference, and mindfulness. In fact, to our knowledge, none of the mindfulness-based trials in MS have measured mindfulness, limiting our understanding of the change process that occurs with training. We stand to benefit most from this work when researchers use the same patient-reported outcome measures so that meaningful comparisons can be made across studies.

The experience of pain is generated by a combination of experiential and neural cognitive, affective, and sensory processes.[41] It is hypothesized that mindfulness meditation modulates the sensory experience of pain by enhancing cognitive control and emotional regulation.[42] In his seminal paper on mindfulness and pain, Kabat-Zinn[12] described how a meditative state (observing experiences as separate from "self") can lead to an uncoupling of thoughts ("It's killing me") and emotions ("I'm scared this will never end") from the sensory experience of pain, thereby reducing hurt and suffering. In line with this theory, experimental brain imaging studies suggest that the neural networks underlying these experiential processes can also be uncoupled by mindfulness meditation.[43] Different meditative practices fall under the umbrella term "mindfulness" (eg, focused attention or open monitoring), each of which activates overlapping yet unique neural networks and can lead to different effects on the pain experience.[42-44] Importantly, even brief training in meditative practice can reduce pain by both experiential and neural mechanisms.[45]

The present data support future investigations of mindfulness-based interventions to reduce pain for people with all types of MS and a wide range of physical abilities. This study has some limitations. The majority of participants were from a single center, and convenience sampling might have led to underrepresentation or overrepresentation of factors in this sample (eg, MS type, MS-related disability); indeed, most of the study sample was white. We did not collect information about socioeconomic status or comorbidities. Fourteen participants experienced fatigue and discontinued the visit before completing the pain interference survey, further complicating our ability to tease out the effect of disability status on the relationship between pain and mindfulness. Nonetheless, our initial findings are closely aligned with other cross-sectional estimates.[33] We predicted mindfulness effects on pain interference, but our cross-sectional design precludes determination of the direction of the observed relationships, and alternative models should not be discounted. Regardless of potential limitations, we found highly significant relationships that we believe merit further study.

In conclusion, the present data show a significant relationship between self-reported mindfulness and pain interference scores in people with MS. Levels of mindfulness are malleable and can be increased by mindfulness training. With the need for more effective approaches to manage MS pain and the recent interest in mindfulness-based interventions, these findings are notable and warrant further exploration. □

PRACTICE POINTS

- Findings from this study suggest a clinically significant association between mindfulness and pain interference in MS.
- Community-based mindfulness interventions are safe and relatively low cost and deserve consideration for people with MS in chronic pain.

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