

# Pain in patients with multiple sclerosis: a complex assessment including quantitative and qualitative measurements provides for a disease-related biopsychosocial pain model

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**Background:** Pain of various causes is a common phenomenon in patients with Multiple Sclerosis (MS). A biopsychosocial perspective has proven a useful theoretical construct in other chronic pain conditions and was also started in MS. To support such an approach, we aimed to investigate pain in MS with special emphasis on separating quantitative and qualitative aspects, and its interrelation to behavioral and physical aspects.

**Materials and methods:** Pain intensity (NRS) and quality (SES) were measured in 38 consecutive outpatients with MS (mean age, 42.0 ± 11.5 years, 82% women). Pain-related behavior (FSR), health care utilization, bodily complaints (GBB-24) and fatigue (WEIMuS) were assessed by questionnaires, and MS-related neurological impairment by a standardized neurological examination (EDSS).

**Results:** Mean pain intensity was 4.0 (range, 0–10) and mean EDSS 3.7 (range, 0–8) in the overall sample. Currently present pain was reported by 81.6% of all patients. Disease duration and EDSS did not differ between patients with and without pain and were not correlated to quality or intensity of pain. Patients with pain had significantly higher scores of musculoskeletal complaints, but equal scores of exhaustion, gastrointestinal and cardiovascular complaints. Pain intensity correlated only with physical aspects, whereas quality of pain was additionally associated with increased avoidance, resignation and cognitive fatigue.

**Conclusion:** As in other conditions, pain in MS must be assessed in a multidimensional way. Further research should be devoted to adapt existing models to a MS-specific model of pain.

**Keywords:** pain intensity, quality of pain, pain-related behavior, bodily complaints, multiple sclerosis

## Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system that often leads to long-term physical disability.<sup>1</sup> Throughout the course of the disease, pain is a common, varying symptom and a significant problem.<sup>2</sup> In 23% of patients with MS, pain was found as part of the presenting symptoms at disease onset.<sup>3</sup> Previous studies have reported remarkable pain prevalences up to 79.4% and 92% in patients with MS.<sup>4,5</sup> Pain in MS patients can be caused directly by inflammatory attack on afferent fiber tracts, or indirectly by various sequelae of MS (eg, limb paresis, extrapyramidal or cerebellar syndromes, bladder dysfunction),<sup>1</sup> leading to increased muscle tone with spasms, postural abnormalities, or urinary tract infections.<sup>2,6</sup> In addition, drug treatment is a potential contributor to pain.<sup>6,7</sup> On

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the other hand, pain in MS influences many aspects of daily living<sup>2,8,9</sup> (eg, important domains of health-related quality of life)<sup>10</sup> and physical activity.<sup>11,12</sup> The consequences of pain in MS should be assessed with a focus on psychosocial aspects – an issue that has received insufficient attention in numerous previous studies.<sup>2,13</sup> The available data suggest that depression, pain behavior, health care utilization, coping behavior, and beliefs might be important determinants of pain.<sup>2,6,13–16</sup> In other painful conditions – such as low back pain – biopsychosocial models, which describe interactions of bodily pain with cognitive, behavioral, and social variables, have proven useful in understanding the complex conditions of the disorder and guiding interventions.<sup>17–20</sup> Kerns et al<sup>6,13</sup> proposed a multidimensional model for pain in MS; amongst others, behavioral aspects have received more attention in this model. For example, muscle weakness can contribute to more generalized deconditioning and increased musculoskeletal complaints; these changes, in combination with fear of pain, contribute to avoidance behavior with a consecutive worsening of muscle weakness and thus additional pain.<sup>6</sup> The usefulness of this analytical process in MS patients was underscored by a recent study by Motl et al,<sup>21</sup> who focused on behavioral aspects, especially physical activity. They found that MS patients who were more physically active had lower scores of pain along with reduced depression and fatigue, as well as improved self-esteem. Comparable data were also presented by Turner et al.<sup>22</sup> Another investigation showed a significant association of pain beliefs and coping strategies with pain intensity scores in patients with MS.<sup>15</sup> Generally, previous studies in MS patients often assessed pain in a dichotomous way, providing the proportion of patients with and without pain.<sup>9–12</sup> This was sometimes supplemented with quantifying pain intensity using rating scales.<sup>5,9–12,16,23</sup> One aspect that has been incompletely addressed – especially in the field of neuropathic pain – is recording both pain intensity and quality of pain.<sup>24</sup>

The aims of the present study were (1) to investigate both pain intensity and quality of pain in MS patients – predominantly in a quantitative modality – and (2) to analyze their interrelations to physical (bodily complaints, fatigue) and behavioral factors (pain-related behavior, health care utilization), exploring the components of a biopsychosocial model applicable to MS.

## Materials and methods

### Study design and population

In a prospective setting, unselected consecutive outpatients attending the Department of Neurology of the University of

Leipzig in 2007 with an established diagnosis of MS were asked to participate in a survey using a standardized paper-and-pencil questionnaire. Data from 49 participants were available; 38 of these subjects provided information about pain and were analyzed.

### Assessments

*Pain intensity* (NRS) was assessed with a numerical rating scale (scaled from 0 to 10)<sup>25</sup> addressing the average pain, which is associated with MS according to the patient's point of view. Thereby, 0 represents no pain and 10 the most painful sensation imaginable. In addition, the lowest and highest intensity of pain were recorded.

*Quality of pain* (SES) was measured by the pain sensation scale.<sup>26</sup> This tool contains 24 adjectives of pain sensation in a questionnaire; each of them is scaled from 1 to 4. Fourteen items comprise the affective dimension, and ten items contribute to the sensory dimension.

*Bodily complaints* (GBB-24) were measured using the short version of the Giessen-subjective complaints list.<sup>27</sup> In this questionnaire patients rate a list of 24 complaints according to currently perceived severity from 0 to 4. The items are attributed equally to four dimensions: exhaustion, gastrointestinal complaints, musculoskeletal complaints and cardiovascular complaints. The total score of complaints equals the sum of the four dimensions. The GBB-24 is one of the most commonly used complaints lists in Germany and was standardized using the German population.<sup>28</sup>

*Fatigue* (WEIMuS) was assessed by the Würzburg fatigue inventory for multiple sclerosis as described by Flachenecker et al.<sup>29</sup> In this questionnaire 17 items (scaled from 0 to 4) are listed, resulting in two dimensions: cognitive fatigue and physical fatigue. The scale combines items from the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) simplifying the partly overlapping scales; it has been validated in a German MS population and found to reflect all aspects covered when administering the separate scales.<sup>29</sup>

*Pain-related behavior* (FSR) was measured with the dimensions avoidance, resignation and distraction of the Questionnaire on Pain Regulation; in each case eight items (scaled from 1 to 7) generate one dimension.<sup>30</sup>

*Health care utilization* reflects the self-reported number of MS-related physician consultations, physician changes, days off work, physical therapies, days of hospitalization and surgical interventions within the last 12 months.

The *severity of neurological impairment* due to MS was quantified by the Expanded Disability Status Scale (EDSS),<sup>31</sup>

the most common scale to measure impairment in MS patients ranging from 0 to 10 in 0.5 increments,<sup>32</sup> around the time of completing the questionnaire.

For all measurements, higher values correspond to higher intensity of each respective dimension.

## Statistical analyses

Questionnaire scores (GBB-24, SES, WEIMuS and FSR) were calculated as rounded means with a tolerance of one missing item per scale. Descriptive statistics were applied for sample descriptions. For differences between two groups, the Kolmogorov–Smirnov test was used. Analysis of Variance (ANOVA) was applied for differences between more than two groups, followed by the Duncan test for multiple comparisons. Relations between variables were analyzed using Pearson's correlations. Data are given as mean  $\pm$  standard deviation, unless otherwise indicated. All calculations were performed with SPSS (v 18.0; SPSS Inc, an IBM Company, Chicago, IL). A  $P$ -value  $<0.05$  was considered statistically significant.

## Results

The present sample of 38 patients with MS consisted of seven men (18.4%) and 31 women (81.6%). Patients' mean age was  $42.0 \pm 11.5$  years (range, 21–69) and all

were native Germans. The mean disease duration was  $8.6 \pm 7.3$  years (range, 1–26). The clinical course of MS was relapsing–remitting in 24 (RR; 63.2%), secondary progressive in seven (SP; 18.4%), and primary progressive in five patients (PP; 13.2%). Two patients (5.2%) suffered from a clinical isolated syndrome of CNS demyelination (CIS). Due to the small number, the latter group was not used for analysis of differences according to the clinical course.

## Pain intensity and quality of pain

Table 1 gives an overview on pain intensity and quality of pain as well as the physical and behavioral aspects. There was no significant difference between men and women for pain intensity (men,  $3.9 \pm 3.0$ ; women,  $4.1 \pm 2.6$ ;  $P = 1.000$ ), nor for sensory (men,  $21.0 \pm 8.9$ ; women,  $16.4 \pm 6.5$ ;  $P = 0.726$ ) or affective dimensions of pain quality (men,  $29.3 \pm 13.0$ ; women,  $26.8 \pm 10.7$ ;  $P = 0.898$ ). Age did not correlate with pain intensity ( $r = 0.14$ ;  $P = 0.390$ ), sensory ( $r = 0.18$ ;  $P = 0.328$ ) or affective ( $r = 0.20$ ;  $P = 0.281$ ) dimensions of pain quality. Course of MS (RR, SP and PP) did not differ with respect to pain intensity, affective or sensory quality of pain ( $P = 0.721$ ;  $P = 0.243$ ;  $P = 0.413$ , respectively). Disease duration was not correlated with pain intensity ( $r = 0.24$ ;  $P = 0.143$ ), affective ( $r = 0.26$ ;  $P = 0.174$ ) or sensory ( $r = 0.14$ ;  $P = 0.470$ ) dimensions of pain quality.

**Table 1** Pain intensity and quality, as well as physical and behavioral aspects in the overall sample

		Mean	Standard deviation	Range
Pain	Pain intensity	4.0	2.6	0–10
	Pain quality			
	Affective dimension	27.1	10.9	14–51
	Sensory dimension	17.0	6.9	9–33
Physical aspects	EDSS	3.7	2.4	0–8
	Bodily complaints			
	Exhaustion	12.0	5.4	0–21
	Gastrointestinal complaints	2.9	2.9	0–12
	Musculoskeletal complaints	10.6	4.2	3–19
	Cardiovascular complaints	3.9	3.3	0–12
	Total score	29.4	12.5	6–55
	Fatigue			
	Cognitive fatigue	13.3	9.4	0–36
	Physical fatigue	17.5	8.6	0–31
Behavioral aspects	Pain-related behavior			
	Avoidance	29.4	10.3	8–47
	Resignation	31.9	10.5	9–50
	Distraction	28.4	9.6	12–51
	Health care utilization (number within the last 12 months)			
	Physician consultations	9.1	5.3	2–25
	Physician changes	0.2	0.5	0–2
	Days off work	58.8	112.8	0–365
	Physical therapies	45.0	68.8	0–260
	Days of hospitalization	6.7	10.2	0–42
Surgical interventions	0.0	0.0	0–0	

## Frequency of pain

Among 38 patients, 31 reported pain intensity above zero. This results in 81.6% of patients experiencing pain at the time of completing the questionnaire. Patients with pain reported MS-related “highest pain intensity” of  $7.1 \pm 2.0$  (range, 2–10) and “lowest pain intensity” of  $2.0 \pm 1.8$  (range, 0–7).

## Differences between MS patients with pain vs no pain

MS patients with pain and those who had no pain were of equal age (pain,  $42.4 \pm 11.4$  years; no pain,  $40.0 \pm 12.4$  years;  $P = 0.871$ ), had comparable neurological impairment (EDSS: pain,  $3.8 \pm 2.3$ ; no pain,  $3.1 \pm 3.1$ ;  $P = 0.556$ ) and disease duration (pain,  $8.9 \pm 7.6$  years; no pain,  $7.3 \pm 6.2$  years;  $P = 0.885$ ). The direct comparisons between the pain and no pain group concerning bodily complaints and fatigue are shown in Figure 1. Those concerning pain-related behavior and health care utilization are illustrated in Figure 2. Significant differences are only apparent for musculoskeletal complaints ( $P = 0.003$ ) and total score of complaints ( $P = 0.033$ ), with higher values for patients with pain. Patients with pain tended to increased avoidance and resignation, and attended fewer physical therapy sessions and had increased days off work, though with no statistical significance ( $P = 0.527$ ;  $P = 0.265$ , respectively).

## Relationship between pain and physical as well as behavioral aspects

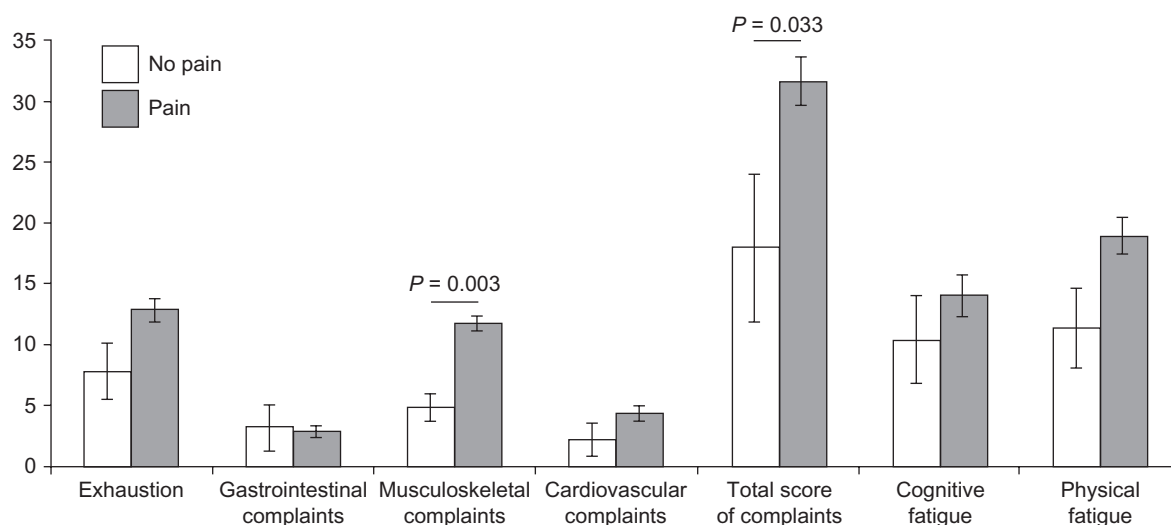
Table 2 shows the interrelation of assessed parameters in terms of a correlation matrix. Pain intensity correlated significantly

with musculoskeletal complaints and consecutively with total score of bodily complaints. A further significant coefficient was found for physical fatigue. Interestingly, there was no significant interrelation to behavioral aspects. The affective dimension of quality of pain was associated with exhaustion and total score of bodily complaints, and furthermore physical fatigue. Concerning behavioral aspects, the affective dimension was significantly correlated with avoidance and resignation. The sensory dimension of quality of pain was significantly associated with physical aspects including all types of bodily complaints and fatigue, but not with severity of neurological impairment (EDSS). A further interrelation was found between the sensory dimension of pain and resignation. Summarizing pain concerning different dimensions, the qualitative aspect of pain was substantially associated with pain-related behavior in contrast to the quantitative dimension. Moreover, pain intensity and quality of pain did not significantly interact with health care utilization (bottom of Table 2).

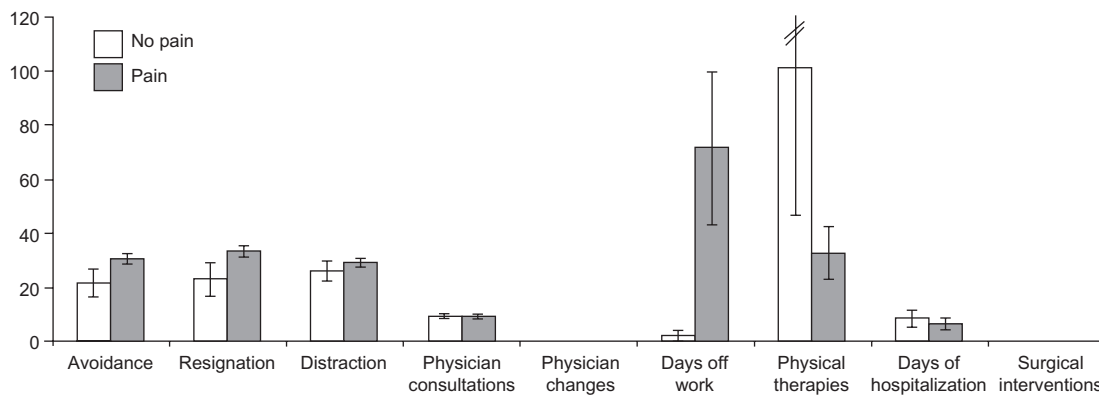
## Discussion

Eighty-one percent of our unselected sample of outpatients with MS suffered from pain at the time of completing the questionnaire. This proportion is comparable with previous studies (eg, 79.4%),<sup>23</sup> although higher (92%)<sup>5</sup> and lower percentages have been reported as well (eg, 42.9% and 66%).<sup>4,12</sup>

Focusing on physical aspects of MS, the means for bodily complaints are increased nearly two-fold for exhaustion, musculoskeletal complaints, and total score of complaints,



**Figure 1** Comparison of physical aspects (bodily complaints and fatigue) between MS patients with and with no pain, displayed as means in bars and standard errors of means in lines.



**Figure 2** Comparison of behavioral aspects (pain-related behavior and health care utilization) between MS patients with and with no pain, displayed as means in bars and standard errors of means in lines.

as compared to the German general population (means: exhaustion, 3.97; musculoskeletal complaints, 5.35; and total score of complaints, 14.03).<sup>28</sup> Cognitive and physical fatigue are nearly equal to values that have been described by Flache-necker et al<sup>29</sup> who validated the WEIMuS scale in 67 patients with MS, which resulted in mean scores of 14.7 for cognitive fatigue and 19.9 for physical fatigue. Pain-related behavior in our sample was remarkably comparable to a group described as “back pain with low competence-estimation”, which was composed of 73 patients and listed in the user manual of the questionnaire (means for comparison: avoidance, 28.34; resignation, 33.21; and distraction, 29.30).<sup>30</sup>

The fact that pain – irrespective of pain intensity or quality – did not correlate with age, disease duration, or severity of impairment due to MS (EDSS) confirms and extends earlier findings,<sup>3,5,10,12,16</sup> though two other studies did obtain positive correlations to age and disease duration,<sup>4</sup> as well as to EDSS.<sup>4,11</sup> However, differing pain assessments and aims might be possible explanations. In detail, Solaro et al<sup>4</sup> recorded presence of neuropathic, somatic, or visceral pain without evaluation of intensity. In contrast, Ehde et al<sup>11</sup> used an 11-point rating scale for pain assessment in a large community sample of MS, but focused on pain-related activity interference, in particular by utilizing an interference numeric

**Table 2** Correlation matrix of pain (intensity, affective and sensory dimension), physical and behavioral aspects in patients with MS

		Pain intensity <i>r</i> (P-value)	Affective dimension of pain quality <i>r</i> (P-value)	Sensory dimension of pain quality <i>r</i> (P-value)
Physical aspects	EDSS	0.23 (0.158)	0.09 (0.639)	0.01 (0.978)
	Bodily complaints			
	Exhaustion	0.32 (0.052)	0.56 (0.001)	0.41 (0.021)
	Gastrointestinal complaints	0.06 (0.747)	0.29 (0.125)	0.40 (0.025)
	Musculoskeletal complaints	0.65 (0.000)	0.35 (0.062)	0.49 (0.006)
	Cardiovascular complaints	0.24 (0.152)	0.17 (0.362)	0.49 (0.006)
	Total score	0.43 (0.007)	0.48 (0.008)	0.56 (0.001)
	Fatigue			
	Cognitive fatigue	0.19 (0.246)	0.24 (0.202)	0.56 (0.001)
Physical fatigue	0.33 (0.044)	0.49 (0.006)	0.53 (0.002)	
Behavioral aspects	Pain-related behavior			
	Avoidance	0.12 (0.496)	0.58 (0.001)	0.35 (0.053)
	Resignation	0.07 (0.695)	0.46 (0.010)	0.36 (0.048)
	Distraction	-0.01 (0.950)	-0.29 (0.125)	0.04 (0.853)
	Health care utilization			
	Physician consultations	0.15 (0.431)	0.41 (0.055)	0.22 (0.314)
	Physician changes	0.09 (0.648)	0.14 (0.540)	0.08 (0.742)
	Days off work	0.36 (0.102)	-0.21 (0.416)	0.22 (0.385)
	Physical therapies	-0.19 (0.330)	-0.03 (0.904)	-0.15 (0.507)
Days of hospitalization	0.00 (0.984)	-0.13 (0.566)	-0.10 (0.644)	
Surgical interventions	-	-	-	

**Notes:** *r*, Pearson’s coefficient; P-value, significance.

rating scale. Notwithstanding these heterogeneous findings, the lack of gender-related differences in pain intensity and quality has been consistently reported.<sup>2,3,11,12</sup>

With respect to a biopsychosocial perspective of pain in MS, it is remarkable that pain was not significantly correlated with EDSS or disease duration. This underscores the need to incorporate physical aspects apart from solely neurological impairment and psychosocial issues. Musculoskeletal complaints were significantly different between the pain and no pain group. This, together with the known predominant pain localization of MS patients – in legs and lower back (74.6% and 59.3%) and neck and shoulders (51.7% and 49.2%)<sup>12</sup> – primarily reflects chronic postural misadjustments. However, the recognition of rather prevalent associations with rheumatoid arthritis and recently with the TNF receptor associated periodic syndrome (TRAPS)<sup>33</sup> add further potentially treatable physical factors. With respect to psychosocial issues, Kerns et al<sup>6,13</sup> especially emphasized cognitive, behavioral and social issues in their biopsychosocial pain model. In line with this extended perspective, Arnett et al<sup>14</sup> recently presented a model of MS-specific depression and thereby pointed out the inconsistent association to physical disability, but supported the use of psychosocial variables (eg, coping and social support). In the behavioral domain, the tendency of increased days off work in patients with pain – which has been found in this study and also by Ehde et al<sup>12</sup> – confirms its socioeconomic consequences in MS.

The differentiated analysis of associations between pain intensity and quality as well as physical and behavioral aspects was performed in the whole sample size, thus representing a quantitative assessment. Overall, more significant coefficients were found for quality of pain when compared with pure pain intensity – this underscores the point of view that pain in MS must be measured by using such differentiated scores, analogous to peripheral neuropathic pain.<sup>24</sup> More specifically, the affective and sensory dimensions of quality of pain had an impact on pain-related behavior, while increasing pain led to augmented avoidance and resignation. The propensity to avoidance is comparable to the mechanisms attributed to chronic low back pain,<sup>18</sup> and suggests that beliefs<sup>19</sup> and coping strategies<sup>15,20</sup> similarly affect pain in MS patients. An increased affective pain dimension, linked to exhaustion and total score of complaints, might lead to avoidance behavior, bodily deconditioning and thus more pain. This postulation proves similar to the model of Kerns et al.<sup>6,13</sup> The additional effect of fatigue due to pain and behavioral avoidance can be inferred from the correlation of both affective and

sensory pain dimensions to fatigue. Such interactions of pain, avoidance and fatigue were also addressed in the biopsychosocial model of Kerns et al,<sup>6</sup> and the connection of pain and fatigue in general has been noted previously.<sup>34</sup> Consistent with this direction, and potentially adding another therapeutic opportunity, is the nonsignificant negative correlation of affective pain and distraction. Exaggerated pain perception due to fear of pain, which can be caused by increased interoception, might prevent patients from seeking distraction from painful sensations.<sup>17</sup> Furthermore, bodily deconditioning and social isolation reduce joyful experience, in turn contributing to affective disorders such as depression.<sup>6,14</sup>

The present study had some limitations: First, the sample size was relatively small, affecting the validity of the study conclusions. Despite this limitation, our study revealed some significant interactions in a biopsychosocial approach of pain in MS, which might be useful in exploring a MS-specific pain model. According to a multifactorial perspective, affective components like depression were not addressed, though these issues of MS are garnering increasing interest in recent years.<sup>14</sup> However, this study was clearly aimed at pain intensity and quality in relation to physical and behavioral factors. Focusing on pain assessment in general, the use of NRS has sometimes been criticized,<sup>35</sup> but sufficiently evaluated tools for multidimensional pain measurement are still lacking.

In summary, physical activity should be encouraged in MS patients with pain in order to prevent bodily deconditioning, secondary fatigue, social isolation and increased pain sensation. This model is supported by the finding that MS patients who are more physically active suffer less from fatigue, pain and depression.<sup>21,22</sup> However, neurological impairment due to MS – eg, spasms or postural abnormalities – often leads to patients avoiding activity and must be taken into account. The therapeutic challenge is to integrate information about individual physical etiology with the analysis of behavioral aspects in an effort to intercept self-amplifying pain mechanisms. Cognitive-behavioral interventions are expected to be useful in this approach.<sup>15,16</sup>

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## Disclosure

The authors have declared no conflicts of interest in this work.

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