

## Pain in multiple sclerosis: A biopsychosocial perspective

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**Abstract**—Clinically significant pain has been found in as many as 65% of persons diagnosed with multiple sclerosis (MS). Acute pain conditions include trigeminal neuralgia, painful optic neuritis, and Lhermitte's syndrome. Chronic pain conditions such as dysesthesias in the limbs, joint pain, and other musculoskeletal or mechanical pain problems develop as a function of spasticity and deconditioning associated with MS. These painful conditions may respond to pharmacological, surgical, rehabilitation, and psychological interventions. However, unresolved pain, associated disability, and affective distress are common. In addition, efforts to manage MS and its associated symptoms, for example, may inadvertently cause osteoporosis and headache or other symptoms that may exacerbate pain and pain-related disability. Conversely, efforts to manage pain may have negative effects on the symptoms of MS (e.g., increased fatigue). A multidimensional approach to assessment and management that is guided by a comprehensive biopsychosocial model is recommended. Such an approach needs to consider the exacerbating nature of MS, MS-related pain, and interventions aimed at their management. Suggestions for future research on MS-related pain conclude the article.

**Key words:** *multiple sclerosis, pain, symptoms, treatment.*

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### INTRODUCTION

Persons with multiple sclerosis (MS) experience a broad array of both acute and chronic pain conditions (1–3). Published reports in the last decade suggest that the prevalence of painful conditions among persons with MS may range as high as 65 percent (4). A significant minority of individuals with MS identifies pain as their most severe symptom (5). Although pain can be managed with a combination of pharmacological and other interventions, the largest proportion of persons reporting MS-related pain suffer from persistent and uncontrollable pain (5). MS-related pain may be directly related to the disease itself and characterized as central pain (e.g., pain associated with optic neuritis and neuralgia), or it may develop secondary to the protracted symptoms of MS (e.g., pain caused by painful muscle contractures and stiffened joints). Unfortunately, pharmacological treatments for MS, such as steroids and  $\beta$  interferons, may also contribute to the development of pain. Furthermore, efforts to manage pain may inadvertently complicate efforts to manage other symptoms of MS.

In contrast to the large and growing literature on the psychosocial aspects of acute and chronic pain conditions, more generally, little empirical research has focused specifically on the effects of MS-related pain on patient functioning and emotional well-being (6). Recent research has documented that MS patients with pain reported poorer mental health and greater deficits in social-role functioning relative to a comparison group of individuals with MS who reported no pain (7). Other

studies suggest that as many as 50 percent of individuals with MS-related pain may have clinical depression (8).

Kerns has proposed that a comprehensive and multidimensional model of chronic pain may be an appropriate perspective for informing the clinical assessment and management of MS-related pain and for guiding future research in this area (6). This model acknowledges the need for careful and thorough investigation of biomedical contributors to nociception and efforts to manage pain itself. The model also argues for simultaneous attention to pain-related disability and affective distress and to psychosocial contributors to the development of persistent pain. In addition, the model encourages the development of a comprehensive, multidimensional, and often, multidisciplinary treatment plan that targets each of these dimensions of the "chronic pain experience" (9).

In this article, we will briefly review the literature documenting the prevalence of pain among persons with MS, the array of specific painful conditions often identified, and strategies that are commonly employed to manage MS-related pain. This will be followed by a consideration of the impact of MS-related pain on psychosocial functioning. Then we will outline a biopsychosocial model of persistent MS-related pain. The model will be used to highlight the complexity of efforts to effectively manage symptoms of MS, including pain, associated disability, and affective distress. A pattern of negative interactions will be highlighted for MS patients in relation to their pain, their caregivers' efforts to manage their pain, and their other symptoms. We will conclude the article with suggestions for future research informed by the model.

## PREVALENCE OF MS-RELATED PAIN

Estimates of the prevalence of pain in MS range from 13 to 80 percent (10). Five relatively recent studies place the estimates at over 50 percent of MS patients. Warnell found that 233 of 364 patients reported pain at some time since the diagnosis of MS, and 40 percent reported that they had chronic, persistent pain (11). Stenager and colleagues assessed 117 MS patients and reported similar findings (5). Sixty-five percent of the participants acknowledged persistent pain (i.e., headache and "minor" acute pain conditions were excluded) at some point since their diagnosis, and 45 percent reported pain at the time of the study. More recently, Archibald and his

colleagues sampled 85 consecutively referred outpatients at an MS research unit and reported a pain prevalence rate of 53 percent, including head pain (7). Nearly 18 percent of this sample reported continuous pain. Indaco and colleagues sampled 141 patients in an outpatient neurology clinic (12). Fifty-seven percent of their sample reported pain at some time during their disease, while 21 percent reported pain at the onset of their disease (13). Collectively, these and other studies document a particularly high prevalence of pain among persons diagnosed with MS and encourage clinical efforts to routinely assess and aggressively manage pain in this population.

These same studies provide some information about the prevalence of specific pain conditions and the distribution of pain problems across disease subtypes. Moulin and colleagues reported that dysesthetic leg pain was the most commonly reported problem, followed by chronic back pain and recurrent painful spasms of the legs (13). Stenager and colleagues attempted to classify painful conditions by diagnosis and presumed cause (5). These investigators reported that the most common among acute pain conditions were neuralgia, Lhermitte's sign, pain associated with optic neuritis, and brief painful tonic spasms. The most frequent chronic pain syndromes were reported to be pain associated with tonic spasms, tension, and painful sensations in the limbs, dysesthesias, and low back pain (5). Indaco and colleagues reported a quite similar distribution of pain as these two previous reports (12). As an alternative approach, Archibald and colleagues categorized pain by four broad body locations (7). Of those reporting pain in at least one site, 53 percent reported head pain, 58 percent reported arm pain, 73 percent reported leg pain, and 49 percent reported pain in the trunk region. Pain was commonly reported to occur in more than one site (76 percent). In addition to these observations, Kassirer has noted that many MS therapies may exacerbate a person's pain (4). She notes that long-term steroid treatment may cause osteoporosis, which can lead to vertebral fractures, and  $\beta$  interferons may cause or exacerbate migraines.

Thus far, no evidence has shown that pain occurs more frequently in any disease subtype, namely relapsing-remitting, relapsing-progressive, chronic-progressive, or benign (7). Only one study could be found that included a comparison group for examination of the extent of pain among individuals with MS. In this study, 35 persons with MS were compared to a matched group

of persons with chronic low back pain. The results indicated that the group with MS reported significantly less pain than the comparison group (14). To date, there is no compelling evidence that the prevalence of pain or type of pain is reliably associated with disease-specific variables, such as the time since onset of MS (i.e., its duration) or indices of severity of MS, or is there consistent evidence of an association between pain prevalence and demographic variables, such as age and gender (5,7,12,13). The one exception appears to be pain associated with neuropathy, which often increases in severity with disease progression (15).

Interestingly, little information is available about the intensity of pain experienced among persons reporting MS-related pain. Vermotte and colleagues reported that pain associated with spasms and neuralgia was the most severe (16). Thirty-two percent of the participants in the Stenager et al. study reported that pain was one of the worst symptoms of MS (5). In only one study reviewed was there an effort to quantify pain intensity with the use of a standardized measure (7). The investigators reported average ratings of pain of 5.8 on a 0 (no pain) to 10 (highest level of pain experienced) numeric rating scale and worst pain severity ratings of 7.7 on the same scale. In this study, pain severity was unrelated to MS duration or symptom severity, number of pain sites, age, or gender.

In conclusion, data convincingly demonstrate a high prevalence of pain among individuals with MS. Much of the pain experienced becomes chronic, although characteristic acute pain conditions are also noted. Multiple pain conditions have been identified as occurring with considerable frequency, and most persons with pain report more than one site of pain. Are there differences in prevalence or type of pain across disease subtypes? remains an important question, and associations with important demographic and disease variables remain unclear. Available data on the severity of pain, although limited, raise concern that pain experienced by these persons is largely uncontrolled and undertreated.

Numerous limitations of the studies reviewed can be cited. These include relatively limited sample sizes and potential sampling biases (e.g., reliance on convenience samples from clinical settings specializing in the treatment of MS). Idiosyncratic methods for assessment of site and diagnosis of pain are common, and most studies failed to employ psychometrically sound measures routinely used in the pain field. There is a strong need for a

large-scale epidemiologic investigation that can help address questions about the prevalence of pain conditions among persons with MS, the distribution of pain conditions across disease subtypes, and relationships of specific pain conditions to important demographic variables (e.g., age, gender, and race).

## MANAGEMENT OF MS-RELATED PAIN

A few reports of medication trials and reviews of common approaches to the pharmacologic management of MS-related pain are available (4,17). Only one published study was identified that reported data on the use of pain medications in this population. Archibald et al. noted that only 29 of 45 participants who reported pain also acknowledged the use of medications for pain, including over-the-counter medications, during the month before study participation (7). Use of analgesics, primarily acetaminophen, was reported by 83 percent of the participants using pain medications, and medications usually used to treat neuropathic pain (i.e., baclofen, carbamazepine, amitriptyline, and phenytoin) were used by 65 percent of the sample. These data are largely consistent with suggestions that MS-related pain may be managed with a conservative medical treatment (17). On the other hand, the low frequency of reported use of narcotic analgesics in this population suggests that narcotics are not effective for central pain. It may also be important to note that over one-third of the individuals evaluated failed to report the use of any medication for pain. One could speculate that several reasons exist why individuals with MS would not report the use of pain medications, including a patient's inability to access pain medications because of being bedridden and the patient's lack of knowledge or interest among practitioners. Under-management of pain conditions has been recently noted to be widespread, and it may be useful to examine more closely whether this is the case among individuals with MS (18,19).

Pharmacological management of pain in MS has its challenges (4). Even aggressive efforts to manage pain in MS commonly fail. For example, carbamazepine may be effective in the early stages of neuralgia, but it may lose its effectiveness over time and alternative medications may need to be added. In some pain conditions with MS, surgical intervention may be indicated when medications fail. Management of painful spasticity may also present a

dilemma, since many persons with MS benefit from some use of spasticity to facilitate standing transfers. Use of newer short-acting medications may be useful in reducing nocturnal spasms, cramps, and spasticity without compromising functioning during the daytime. Strategies for the successful management of optic neuritis continue to be debated in the literature, although the use of an intrathecal baclofen pump appears promising. Management of chronic pain is particularly complicated, and there are no clear guidelines for its pharmacological treatment. Ultimately, ongoing pain is evidently quite common among persons with MS despite growing evidence supporting the effectiveness of several classes of medications.

Rehabilitation approaches may also be helpful in the management of MS-related pain. Soft-collars might help diminish symptoms of Lhermitte's syndrome (17). Physical and occupational therapies that emphasize body mechanics and reconditioning are frequently offered, but little empirical work has been done to confirm the efficacy of these approaches for reducing pain. Kassirer suggests anecdotally that transcutaneous electrical nerve stimulation (TENS) may have some benefit (4).

Despite evidence of the efficacy of psychological interventions, particularly cognitive-behavior therapy, for other chronic pain conditions (20), limited effort has occurred to examine the efficacy of these approaches for pain in MS. One published case study examined the effects of hypnosis on pain in an individual with MS (21). The author reported that sustained use of self-hypnosis contributed to pain relief in the short term, but the examination of longer-term benefits was confounded with the progression of the disease and other rehabilitation efforts. Dane suggested that hypnosis might prove more beneficial if offered along with cognitive-behavior therapy (21). No controlled studies have been done of psychological interventions for pain in MS.

## PSYCHOSOCIAL IMPACT OF PAIN IN MS

A relatively large literature has emerged that examines the psychosocial impact of MS. Individuals with MS have been found to retire from employment early, are more likely to experience clinical depression, are at increased risk for suicide, experience low self-esteem, have lowered perceptions of social support, and have lowered levels of marital satisfaction (22,23). Importantly,

however, existing data also suggest that as many as two-thirds of persons with MS show a positive psychosocial adjustment to MS (24). Several studies have investigated factors that predict poor psychosocial adjustment (24–26).

The specific and incremental effects of pain on psychosocial functioning and emotional well-being are only recently becoming a focus of investigation. In perhaps the best-designed study thus far published in this area, Archibald and colleagues (7) used well-recognized and standardized measures of MS-related disability (Expanded Disability Status Questionnaire) (27) and mental health status (Mental Health Inventory) (28) to examine the impact of pain on these dimensions of psychosocial functioning. Fifty-seven percent of those persons reporting pain indicated that their ability to work had been reduced by 50 percent or more because of pain. Those with pain reported significantly poorer role functioning across each of the domains of sports person, spouse or partner, and friend, as well. Compared to persons without pain, those acknowledging pain reported significantly poorer overall mental functioning. Mean scores on the Mental Health Inventory for those reporting pain fell in the lowest quartile of scores for a normative sample.

Sullivan and his colleagues have published the only controlled study of adjustment to MS that included an examination of the role of pain (14). Groups of 35 persons with either MS or chronic low back pain (CLBP), matched for age, gender, education, and employment status, responded to several standardized questionnaires assessing adjustment to illness and healthcare system use. Regression analyses revealed that illness duration and behavioral coping were significant predictors of healthcare system use for both groups of participants. Illness duration was significantly inversely related to frequency of visits to healthcare professionals. Active behavioral coping, that is, the propensity to plan and initiate action toward problem resolution, was positively related to seeking care. Correlation analyses revealed that higher pain severity was also positively related to extent of healthcare use. Higher pain severity and avoidant coping were, as predicted, significantly associated with greater depressive symptom severity. Comparisons between the two groups revealed that patients with MS, relative to those with CLBP, reported significantly more mobility problems, less pain, fewer additional medical problems, fewer depressive symptoms, and fewer visits to

healthcare professionals. Additional analyses revealed that pain severity accounted for these group differences in healthcare use and depressive symptom severity. Persons with MS acknowledged greater use of cognitive coping, that is, processes related to acceptance, than persons with CLBP. Taken together, these results suggest that, for individuals with MS, the presence and intensity of pain are significant contributors to overall adjustment.

Other researchers in this area have not demonstrated a significant relationship between pain and either disability (12,13) or depressive symptom severity (5,12). The investigation of the role of pain as a contributor to other aspects of psychosocial functioning, such as relationship satisfaction, anxiety, or self-esteem, has not been undertaken.

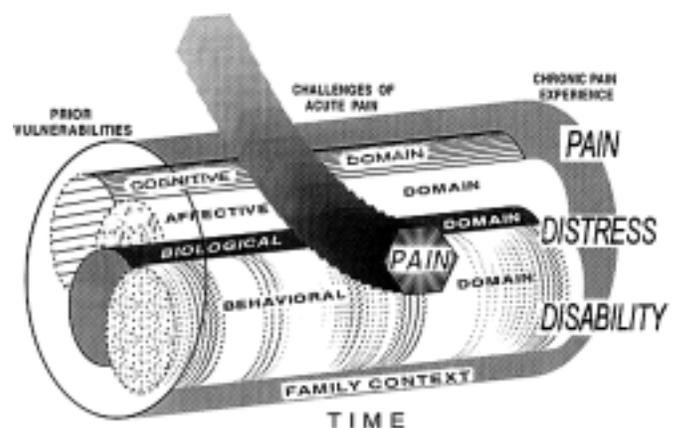
Although it is likely that pain significantly influences physical and psychosocial functioning, limitations in this area of research preclude substantive conclusions at this time. Clearly, further research in this area will be important. Studies designed to tease apart the unique contributions of pain (and interactions of pain with other symptoms of the disease, in the prediction of social-role functioning, emotional well-being, and overall psychosocial adjustment) will be important in informing the development of more effective, comprehensive treatment approaches to MS.

An important area of investigation in the field of pain medicine is the role of psychological and social factors as predictors of pain (29). Although the biomedical contributions to the experience of specific pain conditions in MS are increasingly clear, strong evidence from other areas suggests that the psychosocial context of the experience of pain may play important roles in determining the perpetuation of pain, perceived pain intensity, pain's effects on functioning and emotional well-being, and response to treatment (30). Variables such as distraction, coping style, pain-related fear, anger, and spousal and family members' responses to pain and chronic suffering in general may be particularly fruitful avenues for investigation (31–35). In addition, the extent to which these variables relate to mental status changes, state of disability, magnetic resonance imaging (MRI) findings, use of medications for MS, and stage of MS should be investigated.

## BIOPSYCHOSOCIAL MODEL OF CHRONIC PAIN IN MS

A multidimensional model for understanding the experience of persistent pain may be an appropriate perspective for considering MS-related pain. Such models have proven particularly useful in understanding pain in other chronic painful conditions, and Kerns (6) has recently proposed an adaptation of this perspective for pain in MS. This model is schematically presented in the **Figure**.

According to this model, chronic pain is conceptualized as a multidimensional phenomenon that emphasizes the experience of pain, per se, as well as associated disability and affective distress as equally important dimensions of the “experience of chronic pain” (9). The model is informed by diathesis-stress theory and hypothesizes that numerous vulnerability factors interact with the stress or challenges of the experience of pain (and MS, more generally) to influence adaptation to pain and other symptoms of the disease. In addition to the neurobiological basis of pain, these influences include cognitive, behavioral, and social factors such as those outlined in the previous section. The model also explicitly acknowledges the progressive nature of MS and emphasizes the developmental and dynamic nature of adaptation and adjustment. Finally, the model acknowledges the importance of the social context in which the interactions between vulnerabilities and the stress of MS and pain



**Figure.**

Diathesis stress model of chronic pain (6). Reprinted, by permission, from IASP Press, *Handbook of Health and Rehabilitative Psychology*, 331.

occur, and recognizes the central role of social interactions and social learning in the process of adaptation.

A few examples can help to clarify the model and its relevance for understanding pain in MS and pain-related disability and distress. Muscle weakness, fatigue and, in particular, spasm and spasticity are cardinal features of MS and, as already noted, can be associated with pain. Perhaps an obvious example of the interaction between premorbid functioning and the challenges of MS and pain is the observation that a person with MS who relies on his or her physical integrity for employment and/or important aspects of social-role functioning may experience disability and distress in earlier stages of the disease than another person who has a more sedentary lifestyle and job. This remains a potentially important area for investigation. More subtle examples are equally compelling. Individuals vary in their level of problem-solving competence and confidence. Those who generally avoid problems or who lack skills to cope with some of the everyday challenges of pain and other symptoms of MS may find it difficult to maintain social-role functioning. These individuals may withdraw and avoid activity that may be acutely painful and may, over the longer term, experience more rapid deconditioning, leading to heightened pain and even greater functional limitations. One final example relates to the development of depression, a commonly observed sequela to MS (8,23–26). Persons vulnerable to depression, either neurobiologically or as a function of poor social skills or pervasive negative thinking, may be more likely to develop a clinical depression given the challenges of MS and pain.

The model can also be useful in considering negative interactions that may occur when one symptom or problem associated with MS, or efforts to manage the symptom, inadvertently creates an additional vulnerability for the development or exacerbation of pain. For example, muscle weakness and fatigue associated with MS commonly contribute to more generalized deconditioning and an increased likelihood of the development of joint and muscle pain and peripheral edema. Pain and the fear of making pain worse from activity may contribute to behavioral avoidance and to additional decrements in productive and pleasurable activity. This may subsequently contribute to additional fatigue and muscle deconditioning. In another example, extended use of a wheelchair may place the MS patient at increased risk for low back pain and skin breakdown. A common problem is associated with the long-term use of steroids, which

may contribute to the development of osteoporosis and associated pain (e.g., vertebral fractures) as well as the need for increased bedtime. This may increase the risk for bedsores and additional pain in the already incapacitated patient. Pharmacological management of spasticity and spasms may paradoxically contribute to decreased functional independence (i.e., when a patient loses spasticity after being medicated and falls fracturing vertebrae). It also affects the overall capacity to participate in activities, resulting in further decrements in self-esteem, feelings of competence, and loss of pleasure. These psychological difficulties may be hypothesized to exacerbate existing pain and pain-related disability and distress.

Pain is a frequent complaint among persons with MS, and it is clear that optimal treatment or management of MS requires attention to this problem. The high prevalence of pain encourages routine screening for the presence and intensity of pain in the clinical setting (36). Elicitation of a pain complaint should indicate a more comprehensive assessment of pain, as well as assess potential pain-related interference with social-role functioning and compromised emotional well-being. Clinical assessment informed by a multidimensional model such as the one in this article may lead to greater attention to the complexity of psychosocial factors that can influence the experience of pain and adjustment to pain. A more thorough assessment can inform the development of a more comprehensive, multidisciplinary plan for intervention.

## **DIRECTIONS FOR FUTURE RESEARCH**

There is strong empirical evidence that pain is a prevalent problem among persons with MS. Unfortunately, reliable characterizations of important aspects of pain in MS have only begun to be investigated. Research in this area to date has relied entirely on relatively small samples of patients attending specialized healthcare settings, increasing the likelihood of biases in the collection of data. Such biases may mask important characteristics of pain in MS, such as the distribution of specific pain disorders across disease subtypes; relationships between pain and other disease characteristics; and associations with important demographic and descriptive variables such as age, gender, and race. Given findings from the broader field of pain medicine, examination of the strength of the contributions of pain to MS-related

disability and psychosocial adjustment and adaptation is also critically important targets for investigation.

The integrative model just presented may have heuristic importance by encouraging attention to the complexities of interactions between important biological, psychological, and social variables in determining responses to pain and other symptoms of MS. The need for a large-scale longitudinal epidemiologic study of persons with MS with a specific focus on pain and uncomfortable parasthesias is clearly indicated. Fortunately, such a study has been undertaken and preliminary results are beginning to emerge (37).

There is also a continuing need for even smaller cross-sectional studies of the experience of chronic pain in MS. Little is known, for example, about factors that influence the intensity of pain experienced, the development of pain-related disability and social-role functioning, depressive symptom severity, and overall psychosocial adjustment and adaptation. Studies are needed that investigate the relative contributions of important disease parameters and key psychosocial constructs to the experience of chronic pain in MS. Designs that employ rigorous sampling methods, state-of-the-art measures of key constructs, and sophisticated multivariate statistical procedures are essential.

There is a paucity of controlled trials of rehabilitation (e.g., structured exercise) and psychological treatment (e.g., cognitive-behavior therapy) for pain in MS. Perhaps the lack of such research is understandable given the paucity of research on MS-related pain and the role of psychosocial factors, more generally. Also undoubtedly contributing to the challenge of a controlled trial are factors related to the heterogeneity and complexity of the disease itself (i.e., disease subtypes, type and severity of symptoms, stage of the disease, and cognitive changes associated with disease) and difficulties engaging a sample of persons with MS-related pain large enough to ensure adequate power for examining treatment effects. Nevertheless, such efforts will be important to expanding the availability of these treatments for pain in MS.

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