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Characterizing chronic pain phenotypes in multiple sclerosis: a nationwide survey study

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Abstract

Chronic pain is highly prevalent in multiple sclerosis (MS). Pain heterogeneity may contribute to poor treatment outcomes. The aim of this study was to characterize pain phenotypes distributions in persons with multiple sclerosis (MS), and compare pain phenotypes in terms of pain intensity, frequency of chronic overlapping pain conditions, and use and analgesic effects of different classes of pain medications. Data were collected via a national web-based survey with measures of neuropathic (painDETECT) and nociplastic pain (Fibromyalgia survey criteria), chronic overlapping pain conditions, and pain medication use and pain relief. In a sample of N=842 adults with chronic pain and MS, the largest proportion (41%) showed evidence of nociceptive pain, 27% had mixed neuropathic/nociplastic pain, 23% had nociplastic pain, and 9% had neuropathic pain. Nociplastic pain was associated with significantly higher pain intensity and frequency of chronic overlapping pain conditions. Across all pain types, high frequency of pain medication use along with poor-modest pain relief were reported. Cannabis use for pain was more common and pain relief ratings were higher among those with nociplastic pain, relative to nociceptive pain. Although NSAIDs use was highest among those with nociplastic pain (80%), pain relief ratings for NSAIDs were highest among those with nociceptive pain. These findings underscore the need for multidimensional assessment of pain in MS with greater emphasis on the identification of pain phenotype. An improved characterization of pain as a multifaceted condition in MS could inform therapeutic approaches.

Keywords: *multiple sclerosis, chronic pain, neuropathic pain, nociplastic pain, nociceptive pain*

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that affects approximately one million people in the United States and is the leading cause of non-traumatic disability in young adults [39,40,65,66]. Chronic pain is one of the most common and disabling symptoms in MS [1,14-16,18,24,25,30,36,38,45,47]. Unfortunately, current pain treatments do not provide sufficient or durable pain relief [56,57].

Poor analgesic outcomes may result from pain heterogeneity in MS [17,18,54,55,57]. Many studies have focused on the prevalence of specific pain syndromes in MS (e.g., migraine, trigeminal neuralgia, Lhermitte's sign)[44,54,63], but an approach that focuses on describing pain subtypes with common underlying mechanisms could have greater therapeutic potential [2,13,44,56]. Attempts to characterize pain subtypes often employ time- and resource-intensive approaches to identifying pain mechanisms (e.g., quantitative sensory testing, imaging)[2,13]. Alternatively, survey-based assessments have provided useful information about putative underlying pain mechanisms in populations outside of MS [7,8,23,28,42,64].

The International Association for the Study of Pain (IASP) has defined three categories of mechanistically-based pain types [43,62]. *Neuropathic pain* results from lesion or disease of the somatosensory nervous system [53]. Given the axonal injury associated with MS, pain is often assumed to be neuropathic in origin [27]. *Nociceptive pain*, in contrast, arises from

activation of nociceptors in the periphery due to actual or threatened tissue damage (including inflammation) as opposed to dysfunction in the somatosensory nervous system[26]; nociceptive pain is not well characterized in MS. *Nociplastic pain* arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. This type of pain, often termed "centralized pain" or "central sensitization," is thought to be due to CNS alterations in pain processing, as opposed to ongoing inflammation (nociceptive) or damaged neural pathways (neuropathic)[31,53,62].

To date, the majority of work on pain in persons with MS has focused on pain associated with focal demyelinating lesions [44], with little attention given to concomitant nociceptive/inflammatory or nociplastic mechanisms, or differences in perceived treatment effects related to pain mechanisms. One study of the natural history of pain in MS indicated that those with chronic pain went on to develop more widespread pain over time (a characteristic of central sensitization)[74], but an examination of nociplastic pain in MS has not been undertaken. Work to identify subgroups with different underlying pain mechanisms will likely improve pain outcomes in MS by providing opportunity to tailor therapies to an individual's specific type(s) of pain [2].

To address gaps in knowledge about pain phenotypes in MS, we conducted a nation-wide survey to: 1) characterize distribution of neuropathic, nociceptive, nociplastic, and mixed neuropathic/nociplastic pain in those with chronic pain and MS; 2) examine whether level of pain intensity and prevalence of chronic overlapping pain conditions [37] differ between pain subtypes, with the expectation that both would be higher in those with nociplastic pain [67]; and

3) compare use and perceived pain relief from commonly used pharmacological analgesic treatments.

Methods

Prior to study initiation, the protocol was submitted to the University of Michigan (UM) Medical Institutional Review Board; the study was deemed to meet federal and institutional criteria for exempt human subjects research. Survey data was collected through Qualtrics, a HIPAA compliant online research tool that allows for direct data entry by study participants and provides real-time data export and automated accrual report features [49]. Individuals who completed the survey had the option of entering a raffle to win one of twenty $100 gift cards.

Study Sample

Study inclusion criteria included a self-reported MS diagnosis and age 18 years or older. There were no other inclusion or exclusion criteria, as the goal was to survey a diverse sample of adults with MS from across the US. Participants were recruited through 1) an existing research registry at UM of people with medically documented-MS, 2) posting of the study survey link on the UM research website www.UMHealthResearch.org, and 3) via a National MS Society listserv email, which distributed the survey link nationwide to approximately 79,100 email addresses (~44,000 emails were opened). Data were collected between December 5, 2019 and January 13, 2020.

Measures

The online survey included an in-depth demographic questionnaire (e.g., age, self-reported biological sex and gender, education level, income, marital status, employment status, state of residence) as well the following validated self-report measures. To evaluate the accuracy of self-report of MS, surveys items assessing source of MS diagnosis (e.g., physician specialty), prior diagnostic workups, and current use of disease modifying therapy were also administered.

Neuropathic Pain.

Neuropathic pain was assessed using the painDETECT questionnaire (PD-Q), a 13-item screening survey to determine the presence/severity of pain of neuropathic origin [20]. The PD-Q assesses current average and worst pain intensity over the past 4 weeks (rated on an 11-point numeric rating scale of 0-10) as well as the presence of neuropathic pain qualities (e.g. burning sensation, tingling/prickling sensations; rated on a Likert scale from 0 [never] to 5 [very strongly]). Pain duration/pattern and radiation of pain are also assessed. The total score ranges from -1 to 38, with higher scores indicative of higher likelihood of neuropathic pain origin. Scores ≤12 indicate that a neuropathic component of pain is unlikely, scores between 13 and 18 are ambiguous, and scores ≥ 19 indicate that a neuropathic component of pain is likely.

Nociplastic Pain (Centralized Pain).

The degree of centrally enhanced pain processing was assessed using the American College of Rheumatology (ACR) 2011 Fibromyalgia (FM) Survey Criteria [6,70,71]. This survey includes the number of painful body regions using the Michigan Body Map (0-19) and related symptoms such as problems thinking, fatigue, and sleep difficulties (0-12). This

continuously scaled metric (ranging between 0-31) can be used as a proxy index for central sensitization or can be used to indicate likely fibromyalgia with a cut-point of >13 [71]. This survey has been previously used to quantify centralized pain in other clinical populations [7,28,41], relates strongly to functional neuroimaging findings in nociplastic pain [3,32], and is a robust predictor of both pain and disability [68,69,72,73].

Pain intensity

Pain intensity was assessed with the PROMIS Pain Intensity 3a [10], a 3-item measure that assesses worst and average pain in the past 7 days as well as current pain. The item scores were summed, and the total scale score transformed into a normative T-Score metric, with a Mean=50, Standard Deviation=10. Higher scores are indicative of higher pain intensity.

Chronic Overlapping Pain Conditions.

Measures that screen for three common chronic overlapping pain conditions (migraine, temporomandibular disorders [TMD], pelvic pain) [37] were administered. The three-item ID Migraine™ was used to screen for presence of migraine [34]. Endorsement of at least 2 of the three symptoms (nausea, photophobia, and headache-related disability) has been shown to have excellent sensitivity, specificity, and predictive value relative to identifying migraine as well as excellent test-retest reliability [34]. Presence of likely TMD was assessed with a validated 3-item screening survey, the 3Q/TMD [35]. For this instrument, a score of 3 affirmative responses on two jaw pain items and one jaw dysfunction item indicates a conservative estimate of TMD risk. Presence of pelvic pain was assessed with a single Yes/No item, “Do you have persistent or periodic pain in your pelvis (genitals, pubic, bladder, or perineum region)?”.

Pain Medication Use and Associated Relief

A survey of pain medication use and relief was designed for this study. Current use of cannabinoids for medical purposes was collected. Respondents were also asked to endorse if they had used any of the following medications in the past month to manage any pain that was reported in the survey (selecting all that applied): non-steroidal anti-inflammatories (NSAIDs), opioids, anticonvulsants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), antispasmodics, steroids, and benzodiazepines. For each drug category, a list of example medications was provided on the survey. Respondents rated how much pain relief the medication provided on a 0 (no pain relief) to 10 (complete pain relief) numeric rating scale.

Data Analysis

Demographic and clinical characteristics of the sample were summarized as mean (standard deviation [SD]) and/or median (Interquartile range [IQR]) for continuous variables, and frequency and proportion for categorical variables**.** Chi-squared tests were used to compare frequency of chronic overlapping pain conditions and use of different pain medications by pain subtype group. One-way analysis of variance (ANOVA) was used to compare mean PROMIS pain intensity T-scores and reported pain relief from different pain medications by different pain subtype groups. In cases where the omnibus ANOVA test was significant, post hoc multiple comparison Tukey HSD tests were conducted to examine pair-wise comparisons of pain intensity and pain relief ratings across the pain subtypes. Standardized effect sizes (Cohen's *d*) were calculated to further characterize statistically significant pair-wise group differences.

Results

Preliminary Results

A total of 1,220 individuals representing 49 US states (except Wyoming) and the District of Columbia accessed the survey, indicated an MS diagnosis, and were invited to continue the survey. Analyses were completed on the 842 (69%) respondents who endorsed chronic pain (lasting at least three months) and who had scores (non-missing data) on the painDETECT and FM Survey Criteria. Those whose data were included in the analyses were statistically significantly older ($M_{included}$=51.83±11.98 [standard deviation follows all ± symbols hereafter], $M_{excluded}$=49.77±12.84; F(1,1216) = 7.3, p = 0.007) but were not significantly different in terms of sex distribution (p=0.67). Descriptive statistics for the study sample are in **Table 1**. Distribution characteristics for all variables subjected to ANOVA tests (e.g., PROMIS pain intensity, pain relief scores) met normality criteria for conducting parametric statistical tests (all skew values <|.76|, all kurtosis values <|1.2|).

Distribution of pain subtypes

On the ACR FM Survey Criteria (measure of centralized pain), the sample mean was 12.19±5.65 and the median was 12 (IQR=8,16; See **Figure 1.**). Using the ACR FM Survey Criteria cut-point of ≥13, 346 (41.1%) of the sample scored positive for FM.

For the measure of neuropathic pain, the painDETECT, the sample mean was 15.73±8.18 and the median=16 (IQR=10, 21; See **Figure 2.**). Most of the sample did not show strong evidence of neuropathic pain, with 303 (36.0%) scoring the range indicating an unlikely neuropathic component, 234 (27.8%) scoring in the Unclear/Ambiguous range, and 305 (36.2%) scoring in the likely neuropathic range on the scale.

Using the median score on the ACR FM Survey Criteria (i.e., 12) and the positive cut-point on the painDETECT (≥19) to identify probable pain phenotypes in this sample (**Figure 3**), the largest subgroup showed low scores on measures of both neuropathic and nociplastic pain (n=341, 40.5%) and was labeled "nociceptive type". The next largest subgroup scored high on measures of *both* neuropathic and nociplastic pain (n=226, 26.8%) and was labeled "mixed type". The group that reported pain that did not show neuropathic characteristics but scored high on the FM Survey (n=196, 23.3%) was labeled "nociplastic type". The smallest subgroup, which consisted of people with MS who showed evidence on the painDETECT of probable neuropathic pain but no evidence of nociplastic pain (n=79, 9.4%), was labeled "neuropathic type".

Pain Intensity and Chronic Overlapping Pain Conditions

The pain subtypes differed significantly in terms of PROMIS pain intensity T-scores ($F(3, 841) = 123.11$, $p < 0.001$). The nociceptive type had the lowest (Mean=44.98±6.89) and the mixed neuropathic/nociplastic type had the highest (Mean=55.06±5.77) average pain intensity. The neuropathic (Mean=50.82±6.02) and nociplastic types (Mean=50.71±5.59) had nearly identical average pain scores. Post-hoc multiple comparison tests revealed that all pain subtypes were significantly different from each other in terms of pain intensity scores (all $p < 0.001$), with the exception of no significant difference between neuropathic and nociplastic subtypes ($p = 0.99$; Cohen's $d = 0.02$). Large differences in mean pain scores were observed between the nociceptive and neuropathic (Cohen's $d = 0.90$), nociplastic (Cohen's $d = 0.91$), and mixed pain subtypes (Cohen's $d = 1.58$). Medium effects for mean pain differences were observed between mixed pain and both nociplastic (Cohen's $d = 0.77$) and neuropathic pain subtypes (Cohen's $d = 0.72$).

Migraine was the most common chronic overlapping pain condition, followed by chronic pelvic pain; TMD was relatively rare. Prevalence of chronic pain conditions significantly differed by pain subtype (**Table 2**); in all cases, the mixed neuropathic/nociplastic pain type reported the highest frequency of chronic pain syndromes. Nociceptive type showed the lowest frequency of chronic overlapping pain conditions, with the exception of chronic pelvic pain, for which neuropathic pain type had the lowest frequency.

Pain Treatments

Non-steroidal anti-inflammatory drugs were the most commonly used (66.5%) and steroids the least commonly used (6.5%) medications for analgesia across all pain types (see **Table 3**). For all pain medications, frequency of use significantly differed across the pain subtypes. Participants with high centralized forms of pain – nociplastic or mixed nociplastic/neuropathic pain – most frequently reported use of cannabinoids, opioids, SNRIs, SSRIs, antispasmodics, and benzodiazepines. In contrast, participants categorized with the nociplastic pain type used NSAIDS 10% more frequently than the other groups. For anticonvulsants, those with the nociceptive pain type reported use frequencies~15% lower than the other three groups. Steroid use, although uncommon in general, was highest for those with any type of neuropathic pain – either alone or with nociplastic pain (mixed type).

Narcotic pain medications received the highest average pain relief ratings (Mean=6.99±1.78, Median=7.00, IQR=6,8), followed closely by cannabinoids (Mean=6.29±2.17, Median=7.00, IQR=5,8). SSRIs were associated with least pain relief (Mean=2.72±3.12; Median=1, IQR=0,5) across all pain types. Analgesic ratings significantly differed by pain subtype for only two classes of medications: relief ratings for cannabinoids were

significantly higher for those with mixed pain compared to neuropathic pain (Tukey's HSD p = 0.02; Cohen's d = 0.65), and relief ratings for NSAIDS were significantly higher for those with nociceptive pain compared to nociplastic (p = 0.001; Cohen's d = 0.41) and mixed pain subtypes (p < 0.001; Cohen's d = 0.70) and for those with nociplastic pain compared to mixed pain (p = 0.04; Cohen's d = 0.30). Comparisons of pain relief ratings for benzodiazepines were underpowered due to low frequency of use and did not reveal statistically significant differences, despite substantial mean differences, indicating that the neuropathic type rated this class of drugs 2.32 points higher in terms of pain relief relative to nociceptive type (Cohen's d = 0.82), 2.84 points higher relative to nociplastic type (Cohen's d = 1.02), and 1.96 points higher relative to mixed pain type (Cohen's d= 0.78) on the pain relief scale.

Discussion

This is the first study to characterize pain phenotypes in MS within the IASP-defined mechanistically-based framework, and to compare pain phenotypes in terms of pain intensity, chronic overlapping pain conditions, and use of/perceived analgesia of commonly used pharmacological therapies. The pattern we identified in MS is similar to that seen with other autoimmune disorders [12,46], where nociceptive pain is the most common underlying pain descriptor but a sizable proportion of individuals also have nociplastic or mixed neuropathic/nociplastic pain types. In this sample, it was relatively uncommon for individuals to score high solely on the measure of neuropathic pain while not also scoring high on the measure of nociplastic pain. This suggests that identification of neuropathic pain alone may be insufficient to fully characterize pain for many individuals with MS, who may also demonstrate features of co-occurring nociplastic pain.

Nociceptive pain has been recognized as one pain subtype in MS, often associated with postural problems, deconditioning, and/or muscle spasms [52,57]. However, the prominent focus on neuropathic pain in MS has contributed to lack of understanding of the scope and nature of nociceptive pain in MS. Given the relatively high prevalence of nociceptive pain in our sample (41%; indicated by neither neuropathic nor nociplastic pain characteristics), it is critical to gain a better understanding of nociceptive pain with an eye toward optimizing treatment for this pain subtype. Identification of patients with primarily nociceptive pain could enhance the chance of analgesic success. It is important to note that, due to our process of identifying nociceptive pain by process of elimination from the other pain categories, we may have underestimated the proportion of our sample with of pain of nociceptive origin; it is likely that mixed pain in MS also includes overlap of nociceptive pain with neuropathic and/or nociplastic in the same individual [19,21,61].

Nearly 60% of the sample had evidence of predominantly nociplastic pain, neuropathic pain, or a combination of both. This finding is not surprising, given the widespread CNS damage associated with MS and associated changes to the somatosensory system and pain processing. Yet, while neuropathic pain is commonly studied in MS, there have been no known investigations of centralized (nociplastic) pain, as it is currently defined, in MS. However, allodynia, perceived pain in response to a non-painful stimuli and a common feature of centralized pain, has been previously identified in patients with MS and chronic pain [58,59]. Further examination of two likely scenarios of nociplastic pain in MS – nociplastic pain occurring prior to the onset of MS or nociplastic pain developing after onset of MS – is warranted; in particular, examination of possible contributions of MS CNS lesions to central sensitization and pain centralization is needed to better understand and treat pain in MS.

Results for pain intensity and overlapping pain conditions were consistent with our expectations. We found a graded increase in pain intensity when going from the group with nociceptive pain to those with elements of nociplastic pain. This is expected as nociplastic pain is thought to be due to CNS pain sensitization/amplification, and this same finding is noted when phenotyping based on pain mechanisms in rheumatic and other autoimmune disorders [5,7]. Also as expected, chronic overlapping pain conditions were reported more frequently in those with nociplastic pain type. Though these pain conditions are diagnostically distinct, they share many similar characteristics (e.g., fatigue, mental fog, sleep problems), frequently co-occur, and are considered to be different manifestations of a common cause – pain amplification due to central sensitization [37,67]. This consideration highlights an understudied overlap between characteristics of MS and chronic overlapping pain conditions, including FM. Significant problems with chronic pain, fatigue, cognitive dysfunction, depressed mood, and poor sleep are shared features of both MS and FM. The measure of pain centralization, the ACR FM survey criteria, includes a number of these symptoms – fatigue, sleep, and cognition - in the calculation of the total score. This overlap could complicate the interpretation of FM survey criteria scores in a sample of people with MS. It is possible that classification of degree of central sensitization and classification of "positive" FM cases are overestimated because of this similarity in symptomology. It is also plausible that a significant proportion of people with MS truly have nociplastic pain, with some of these having a diagnosis of comorbid FM. Given our de-emphasis of identifying specific syndromes, we would argue for more of a focus on detecting elements of central sensitization mechanisms rather than on the FM diagnosis *per se* [69].

This study has important clinical value, laying the foundation for improving our ability to define individual sensory profiles that may predict differential treatment response. A number of

efforts are underway to advance personalized pain therapy by phenotyping pain using the painDETECT [22,51], and painDETECT scores have been shown to predict treatment response in diabetic neuropathy[4] and chronic low back pain[50]. Similarly, prior research has shown that scores on the FM survey predict outcomes following knee or hip arthroplasty[8] and opioid consumption following surgery[28,33]. Nociplastic pain conditions such as FM are not thought to be responsive to NSAIDs or other anti-inflammatory drugs, and instead preferentially respond to centrally acting analgesics such as gabapentinoids, tricyclics, serotonin norepinephrine reuptake inhibitors, and cannabinoids [11]. Our findings are partially consistent with these previous observations. We found greater self-reported analgesic effectiveness from NSAIDS for nociceptive pain type and from cannabinoids for mixed pain and neuropathic types. Armed with this information, clinicians may be supported in identifying the most appropriate initial pharmacotherapy treatment plan for the presenting pain picture. For example, successfully identifying pain of nociceptive origin spares the patient medications indicated for neuropathic pain that may offer an unfavorable benefit/risk profile. Given that patients with MS are 5 times more likely to receive a neuropathic pain medication than patients without MS [9], identifying those for whom this type of pain medication is not indicated seems particularly critical. Across pain phenotypes, survey responses indicate high utilization of multiple classes of analgesic medication to manage chronic pain in MS and ratings that suggest poor to modest pain relief across the medication categories. NSAIDs have been used for musculoskeletal pain or to address pain flares during MS exacerbations, but are more often indicated as co-medications with other analgesic categories that target neuropathic pain [48,57]. Higher use of cannabinoids in those with nociplastic pain either alone or along with neuropathic pain (mixed pain), is consistent with previous findings that people with MS who demonstrated sensory disturbances indicative of pain

centralization reported higher use of cannabis [52]. Although these initial findings indicate that medications may have different analgesic effects based on pain phenotype, the ability to predict treatment response from survey scores needs to be tested in MS.

This study focused on pharmacological pain treatments, but pain phenotypes could respond differently to physical and psychological therapies as well. The nociceptive-dominant pain subgroup may be driven by a variety of musculoskeletal or inflammatory nociceptive sources of pain that historically respond well to non-pharmacological management approaches, including physical or occupational therapy, that target biomechanical pain generators. There is mounting evidence supporting the effectiveness of psychological therapies to manage symptoms in both MS and FM and demonstrating that psychological interventions can alter how the brain processes sensory information [29,60]. Together these bodies of literature support a shared CNS mechanism of pain in both MS and FM and suggest a need for future research to investigate if and how non-pharmacological treatments may be effective for nociplastic pain in people with MS and chronic pain.

Study Strengths and Limitations

The large nationwide sample, use of validated measures, good response rate, and low level of missing data from those who started the survey are strengths of this study. The sample was predominantly female and white, which limits generalizability. Use of the National MS Society email listserv to recruit most study participants may also limit the generalizability of the findings. Given the lack of available measures to identify nociceptive pain, this pain type was identified by exclusion, which limited our ability to understand mixed pain characterized by co-occurrence of nociceptive and other pain types. The current IASP definition of pain includes

both sensory and emotional aspects of the pain experience; the focus of this paper to attempt to characterize the biological and neurobiological mechanisms of chronic pain in MS does not incorporate potential emotional facets of pain phenotypes. Future research that characterizes MS pain phenotypes based on both sensory and emotional characteristics, and in the context of other symptoms, may help to further clarify our understanding of pain in MS and how best to treat it.

Conclusion

Results suggest that people with chronic pain and MS most commonly experience pain that has characteristics of nociceptive mechanisms or a mixed pain state, which can be described as a combination of nociceptive, nociplastic, and/or neuropathic pain characteristics. Pain that can be described as having purely neuropathic characteristics was relatively rare. This work highlights the need to assess pain phenotype in persons with chronic pain and MS to move toward a precision model of pain management in MS.

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Figure Captions.

Figure 1. Distribution of FM Survey Criteria Scores (N=842)

Figure 2. Distribution of painDETECT scores (N=842)

Figure 3. Distribution of pain types based on surveys of neuropathic and nociplastic pain (N=842).

Table 1. Sample descriptive statistics (N=842)

Sex N (%)	
Male	168 (20.0%)
Female	674 (80.0%)
Gender N (%)	
Male	168 (20.0%)
Female	672 (79.8%)
Transgender	1 (0.1%)
Gender variant / non-conforming	1 (0.1%)
Race N (%)	
White	768 (91.2%)
Black or African American	43 (5.1%)
American Indian or Alaska Native	4 (0.4%)
Asian	6 (0.7%)
Native Hawaiian or other Pacific Islander	1 (0.1%)
Bi /multi-racial	11 (1.3%)
MS type N (%)	
Relapsing remitting	561 (66.6%)
Secondary progressive	137 (16.3%)
Primary progressive	78 (9.3%)
Progressive relapsing	19 (2.3%)
Not sure	47 (5.6%)
Time since MS diagnosis N (%)	
<1 year	50 (5.9%)
1-5 years	183 (21.7%)
6-10 years	164 (19.5%)
11-15 years	147 (17.5%)

16-20 years	125 (14.8%)
>20 years	173 (20.5%)

Table 2. Comparison of frequency of chronic overlapping pain conditions by pain subtype

	Full Sample	Nociceptive Type	Neuropathic Type	Nociplastic Type	Mixed Type	Chi-Squared
Migraine Headache	39.8% (N=842)	33.2% (N=341)	39.6% (N=79)	58.2% (N=196)	67.2% (N=226)	$X^2(3, 841)=55.97$, p <0.001
TMD	3.2% (N=840)	0.6% (N=341)	1.3% (N=78)	3.6% (N=196)	28.2% (N=225)	$X^2(3, 840)=22.22$, p <0.001
Chronic pelvic pain	23.0% (N=837)	13.2% (N=340)	9.0% (N=78)	27.2% (N=195)	39.7% (N=224)	$X^2(3, 837)=63.94$, p <0.001

Table 3. Differences by pain subtype in reported use of pain medications within the past month, and related level of perceived pain relief on 0-10 numerical rating scale

	Nociceptive Type	Neuropathic Type	Nociplastic Type	Mixed Type	Group Comparison Statistic
Cannabinoids	17.9% (N=341)	20.3% (N=79)	28.6% (N=196)	30.5% (N=226)	$X^2(3, 842)=15.13$, p =0.002
Mean(SD) pain relief	$5.87(2.34)_{A,B}$	$5.21(2.67)_{A}$	$6.39(1.93)_{A,B}$	$6.75(2.02)_{B}$	$F(3,237) = 3.75$, p =0.01
NSAIDS	71.4% (N=304)	70.3% (N=74)	80.0% (N=185)	69.4% (N=206)	$X^2(3, 763)=20.85$, p <0.001
Mean(SD) pain relief	$5.88(2.45)_{A}$	$4.98(2.77)_{A, B, C}$	$4.89(2.40)_{B}$	$4.16(2.14)_{C}$	$F(3,556) = 15.45$, $p < 0.001$
Opioids	11.5% (N=304)	13.9% (N=72)	19.5% (N=185)	28.2% (N=206)	$X^2(3, 767)=24.02$, p <0.001
Mean(SD) pain relief	7.23(1.52)	7.80(1.32)	7.00(1.84)	6.71(1.96)	$F(3,139) = 1.38$, $p = 0.25$
Anticonvulsants	25.0% (N=304)	45.8% (N=72)	38.9% (N=185)	44.7% (N=206)	$X^2(3, 767)=26.45$, p <0.001
Mean(SD) pain relief	5.99(2.83)	5.79(2.49)	5.67(2.33)	5.24(2.47)	$F(3,271) = 1.25$, $p = 0.29$

SNRIs	10.6% (N=303)	8.3% (N=72)	17.9% (N=184)	22.5% (N=204)	$X^2(3, 763)=17.17$, p <0.001
Mean(SD) pain relief	5.32(2.49)	4.83(2.99)	4.18(2.57)	4.43(2.99)	$F(3,115) = 1.04$, $p = 0.38$
SSRIs	16.8% (N=303)	11.1% (N=72)	28.3% (N=184)	23.5% (N=204)	$X^2(3, 763)=14.12$, p =0.003
Mean(SD) pain relief	2.82(3.39)	3.43(3.78)	2.06(2.84)	3.21(2.98)	$F(3,154) = 1.30$, $p = 0.28$
Antispasmodics	30.7% (N=303)	33.3% (N=72)	44.0% (N=184)	52.9% (N=204)	$X^2(3, 763)=27.72$, p <0.001
Mean(SD) pain relief	5.88(2.26)	5.71(2.91)	5.63(2.29)	5.57(2.15)	$F(3,304) = 0.33$, $p = 0.80$
Steroids	3.0% (N=303)	11.1% (N=72)	8.2% (N=184)`	11.3% (N=203)	$X^2(3, 762)=15.16$, p =0.002
Mean(SD) pain relief	5.78(3.27)	5.88(2.85)	5.33(2.96)	5.78(2.94)	$F(3,54) = 0.09$, $p = 0.97$
Benzodiazepines	11.6% (N=303)	11.1% (N=72)	18.5% (N=184)	24.0% (N=204)	$X^2(3, 763)=15.79$, p =0.001
Mean(SD) pain relief	4.31(3.24)	6.63(2.33)	3.79(3.17)	4.67(2.66)	$F(3,125) = 2.11$, $p = 0.10$

Note. $_{A, B, C}$ = Values with different subscripts indicate significant pair-wise mean differences. NSAID = non-steroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor