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Cannabinoid use among Americans with MS: Current trends and gaps in knowledge

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Abstract

Background: Up-to-date information regarding the scope and impact of cannabinoid use among persons with MS (PwMS) is necessary to guide clinical practice and cannabinoid research.

Objectives: To assess utilization patterns and perceived impact of cannabinoid use among a national cohort of PwMS.

Methods: Data collected were part of a nationwide survey to characterize pain in PwMS. Items included questions about current/recent cannabinoid use, reasons for use, preferred THC/CBD formulations, and perceived benefits/side effects. PROMIS short-forms assessed symptom severity. Pain phenotype was assessed with the painDETECT questionnaire and FMSurvey Criteria Questionnaires.

Results: Among n = 1,027 respondents, 42% endorsed recent cannabinoid use, of which 18% endorsed healthcare provider guidance regarding use. PROMIS scores (except cognitive abilities), and pain centralization and neuropathic pain scores, were higher among recent/current users (each $p < 0.0001$). Sleep and pain were the most frequently reported reasons for use. Benefit from cannabinoids for sleep and pain were strongly correlated ($r = 0.65$, $p < 0.0001$). For those who expressed a preference for specific THC/CBD ratios, CBD-predominant formulations were favored.

Conclusion: Cannabinoid use is common in PwMS, despite a paucity of provider guidance. The range of perceived benefits, and potential differential effects of THC and CBD, highlight the need for personalized, evidence-based guidelines regarding cannabinoid use.

Keywords: Multiple sclerosis, cannabinoids, cannabis, pain, insomnia, sleep disturbance

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Introduction

A pervasive challenge in MS care is the successful management of several prevalent, chronic symptoms that have an insufficient number or quality of treatment options. This includes chronic pain, which affects over 50% of persons with MS (PwMS), yet remains one of the most challenging symptoms to treat.[1,2] Pain is also frequently associated with sleep disturbances, which affect at least 60% of PwMS,[3,4] and are independently linked to fatigue and other chronic symptoms.[4,5]

Given the high prevalence of pain, sleep disturbances, and overlapping comorbid symptoms,[6,7] and lack of sufficiently effective treatment options, interest in the therapeutic potential of cannabinoids for PwMS has increased. This interest has been further galvanized by changes in cannabis legislation in many states, which has resulted in a rapid rise in consumer use of these compounds,[8] particularly cannabidiol (CBD) – a compound that has been classified as safe and without abuse potential per the World Health Organization.[9]

Despite growing public support for clinical use of cannabis-based treatments in MS, evidence that suggests benefits for central pain and spasticity, and potential benefits for sleep disturbances,[10–13] specific guidelines regarding how cannabinoid use should differ based on underlying clinical phenotype

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or other comorbid symptoms are scarce. In a position statement, the American Academy of Neurology described "*an urgent need to determine the safety and potential benefit of various forms of marijuana for neurological disorders…*" (AAN.com, 2014) However, the design of studies to investigate potential benefits and harms of cannabinoids in PwMS must be informed by the scope and trends in consumer use of these compounds, and areas of greatest decisional uncertainty surrounding clinical use.

Current information regarding real-world patient experiences – including national prevalence estimates of cannabinoid use, factors associated with selection of specific formulations [including CBD and THC], and perceived benefits and side effects – has the potential to guide clinical practice and much-needed research on the benefits and harms of cannabinoid use for common MS symptoms, including pain and sleep disturbances. The objectives of this study were to: 1) Assess the prevalence of cannabinoid use within a national cohort of PwMS in the US; 2) Describe differences in THC and CBD use among cannabinoid users with MS; 3) Explore the current impact of healthcare provider guidance on cannabinoid utilization and 4) Determine associations between cannabinoid use and symptom severity in PwMS, with a focus on pain and sleep disturbances. We hypothesized that cannabinoid users would favor formulations that contained a higher ratio of CBD relative to THC for the treatment of sleep disturbances and pain, and that the majority of cannabinoid users would be using these substances without guidance from their healthcare providers.

Materials and methods

Participants/data sources

These data were collected as part of a parent nationwide survey project to characterize pain subtypes (neuropathic and/or nociplastic pain) and pain treatments in PwMS. This survey was distributed locally (Ann Arbor, MI) through an existing participant registry of patients from the University of Michigan (in which individuals who are interested in research opportunities have given permission to be contacted and invited to participate in projects for which they are eligible), the University of Michigan human subject research website (UMHealthResearch.org), and nationally by an email invitation sent by the National Multiple Sclerosis Society (NMSS) to individuals with MS on their listserv. Volunteers had to endorse a diagnosis of MS and be at least 18 years old. Approximately 79,100 invitations were emailed to eligible participants, who were informed of the objective of the survey in the email solicitation. Survey responses were captured with Qualtrics between December 5, 2019, and January 13, 2020. The survey and protocol were approved by the NMSS and deemed exempt by the Institutional Review Boards of the University of Michigan Medical School (IRBMED).

To ensure the likelihood of diagnostic accuracy of MS, survey items also included questions regarding source of diagnosis (such as physician specialty), prior diagnostic workup, and current disease modifying therapy use. Additional MS-specific items included MS subtype, and time since diagnosis. Disability was assessed with the Patient Determined Disease Steps (PDDS)[14] – a single item measure that asks respondents to select a single category that best describes their function, an 8-point ordinal scale from 1–8 (mild disability-bedridden).

Cannabinoid-related survey items included questions about: 1) current cannabinoid use or prior cannabinoid use in the past year; 2) purpose (medical, recreational, or both); 3) target symptoms; 4) method of delivery (inhaled, oral, or topical formulations); 5) frequency of use; 6) source(s) of information regarding cannabinoid use; 7) preferred THC:CBD ratio for those who expressed a preference (high THC/low CBD, high THC/high CBD, low THC/high CBD, low THC/low CBD, THC monotherapy, CBD monotherapy, or other); and 8) side effects ("Which of the following side effects do you experience from using cannabis/marijuana? [check all that apply"]).

Numeric rating scales (0 = none; 10 = extreme or complete relief) were used to quantify perceived benefits of cannabinoid use on select symptoms, which were queried based on their prevalence in MS and their general association with cannabinoid use (e.g., How much pain relief does cannabis provide? 0 = no pain relief – 10 = complete pain relief; How much does cannabis help with sleep? 0 = not at all – 10 = extremely helpful for sleep). Respondents were not required to provide a numeric rating if they did not experience the particular symptom assessed by that item.

Respondents who endorsed sleep as responsive to cannabinoids were also asked to report specific sleep symptoms that improved with cannabinoid

use (selecting all that applied). Listed symptoms included difficulty with sleep onset, sleep maintenance, achievement of restorative sleep, or sleep quality due to pain.

Seven short-forms from the Patient Reported Outcomes Measurement Information System (PROMIS) were also administered: Pain Intensity-3a,[15] PROMIS Pain Interference-8a,[16,17] PROMIS Depression-8a,[18] PROMIS Anxiety-8a,[19] PROMIS-Fatigue$_{MS}$ Short-Form,[20] PROMIS Sleep Disturbance-8b, and PROMIS Cognitive Abilities-8a.[21] For all short forms, item scores were summed, and the total scale score transformed into a normative T-Score metric, (mean = 50, standard deviation = 10). Higher scores are indicative of higher levels of the measured construct.

Presence of neuropathic pain was assessed using the painDETECT questionnaire (PD-Q),[22] in which scores range from -1 to 38, with higher scores indicative of higher likelihood of neuropathic pain origin. Scores $\leq$12 indicate that a neuropathic component of pain is unlikely, scores between 13-18 are ambiguous; and scores $\geq$19 indicate that a neuropathic component of pain is likely. Degree of CNS pain amplification (i.e., level of nociplastic pain) was assessed with the American College of Rheumatology 2011 Fibromyalgia Survey (FMSurvey) Criteria.[23] Scores range from 0-31 and higher scores indicate higher pain centralization. This survey has been useful to quantify centralized pain in other clinical populations beyond fibromyalgia.[24]

Statistical analyses

Summary statistics for demographic, clinical, and cannabinoid use characteristics are presented as mean and standard deviation (SD) for continuous variables that exhibited a normal distribution, median and interquartile range for continuous variables that exhibited a non-normal distribution, and frequency and percentage for categorical variables. Symptom severity (PROMIS measures), pain subtype, and sleep disturbances were compared between cannabinoid users vs. non-users with t-tests, Chi-squared tests, Wilcoxon rank-sum tests or Kruskal-Wallis rank tests as appropriate. Comparisons of symptom severity, pain phenotype, and perceived sleep benefits among those who used CBD- vs THC-predominant formulations were conducted using one-way analysis of variance tests (with Tukey post-hoc tests where indicated), Chi-squared tests or Fisher's exact tests. For these analyses, respondents who preferred CBD monotherapy or CBD-predominant formulations, and THC monotherapy or THC-predominant formulations were collapsed into single groups.

Results

Of n = 1,234 people who accessed the online parent pain survey, 14 did not endorse an MS diagnosis, and 3 who did endorse an MS diagnosis did not provide responses to other survey items. Data from a maximum sample size of n = 1,217, representing 49 US states (no response for Wyoming) and the District of Columbia, were included in the analyses. The mean number of respondents per state was 24. Michigan, California, and Texas had the highest number of respondents (101, 84, and 71 respondents respectively), while West Virginia, North Dakota, and Hawaii had the lowest number (3, 2, and 1 respondent respectively).

Demographics and clinical characteristics are summarized in Table 1. Mean age was 51.2. The majority of respondents were biologically female and Caucasian. Sixty-nine percent described themselves as having the relapsing-remitting subtype, and 90% reported that their MS diagnosis was rendered by an MS specialist/neurologist. Median PDDS score was 2. Eighty percent were currently using a disease modifying therapy.

Of n = 1,217 survey respondents with an MS diagnosis, n = 1,027 (84%) answered the question about whether or not they had used cannabis in the past year (Table 2). Among these, n = 427 (42%) endorsed cannabinoid use in the past year. Among those reporting cannabinoid use in the past year, 90% (n = 386) used cannabinoids either strictly for medical purposes, or for both medical and recreational purposes. Fifty-nine percent (n = 254) were current users. The majority of respondents who used cannabinoids for medical purposes indicated that their own independent research, or advice from family members/peers influenced their choice to use it. Only 18% discussed cannabinoids for MS symptoms with a health care provider, and less than 1% received assistance from their provider regarding selection of cannabinoid formulations. Frequency of use, preferred THC/CBD ratios, methods of use, magnitude of perceived benefit, and side effects are listed in Table 2. Of 427 respondents who endorsed cannabis use in the past year, N = 188 (44%) expressed a specific THC/CBD ratio preference, while n = 177 (41%) were unsure (Table 2).

Table 1. Demographic and baseline factors.

Age	
Mean (SD)	51.2 (12.3)
Missing data	1 (0.08%)
Biological sex at birth N (%)	
Male	239 (19.6%)
Female	978 (80.4%)
Gender identification N (%)	
Male	239 (19.6%)
Female	974 (80.0%)
Transgender	1 (0.08%)
Gender variant/non-conforming	1 (0.08%)
Missing data	2 (0.2%)
Race N (%)	
White	1077 (88.5%)
Black or African American	65 (5.3%)
American Indian or Alaska Native	4 (0.3%)
Asian	7 (0.6%)
Native Hawaiian or other Pacific Islander	1 (0.1%)
Bi/multi-racial	22 (1.8%)
Missing data	41 (3.4%)
Ethnicity N (%)	
Hispanic or Latino	63 (5.2%)
Not Hispanic or Latino	1070 (87.9%)
Not reported/unknown	53 (4.4%)
Missing data	31 (2.6%)
How was MS diagnosed?[a] N (%)	
MRI scan	1066 (87.6%)
Spinal tap	637 (52.3%)
Evoked potential studies	211 (17.3%)
Other	103 (8.5%)
Time since MS diagnosis N (%)	
< 1 year	69 (5.7%)
1–5 years	262 (21.5%)
6–10 years	242 (19.9%)
11–15 years	202 (16.6%)
16–20 years	169 (13.9%)
> 20 years	250 (20.5%)
Missing data	23 (1.9%)
MS type N (%)	
Relapsing remitting	836 (68.7%)
Secondary progressive	176 (14.5%)
Primary progressive	103 (8.5%)
Progressive relapsing	22 (1.8%)
Not sure	62 (5.1%)
N	1199
Missing data	18 (1.5%)
Who diagnosed MS? N (%)	
Neurologist/MS specialist	1089 (89.5%)
Physiatrist (rehabilitation doctor)	1 (0.1%)
Primary care provider (MD, NP, PA)	59 (4.9%)
Other	50 (4.1%)
N	1199
Missing data	18 (1.5%)
Patient-determined disease steps	
Median (IQR)	2 (1, 4)
Missing data	28 (2.3%)
Disease modifying therapy N (%)	
Yes	972 (79.9%)
No	231 (19.0%)
Not sure/prefer not to say	4 (0.3%)

[a]Respondents allowed to check more than 1 option.

For those who expressed a preference, the majority preferred CBD-predominant formulations.

Compared to cannabinoid non-users, respondents who endorsed cannabinoid use over the past year were more disabled. Cannabinoid use in the past year was associated with significantly higher median PROMIS pain intensity (52.1 vs. 46.3), higher pain interference (60.8 vs. 57.4), higher depression (56.8 vs. 52.1), higher anxiety (55.4 vs. 52.1), higher fatigue ((60.4 vs. 57.3), all $p < 0.0001$) and higher sleep disturbance T-scores (53.3 vs. 52.2, $p = 0.04$), and lower cognitive abilities score (42.8 vs. 45.1, $p < 0.0001$, not shown in table). Cannabinoid use over the past year was associated with higher pain centralization score, and positive screen for neuropathic pain (all $p < 0.0001$, not shown in table). Self-reported activity levels did not significantly differ by cannabinoid use. When evaluating current users only (versus no recent use), each of these results were maintained.

Pain and sleep were the most commonly endorsed reasons for use (Table 2). Mean impact ratings of cannabinoids on each symptom, assessed using numerical rating scales (0 = no relief, 10 = extreme relief), ranged from 6.1 to 8 across the sample (Table 2 and Figure 1). NRS impact scores for sleep and pain relief were highly correlated ($r = 0.65$, $p < 0.0001$).

Among recent cannabinoid users who used cannabinoids to help with sleep (n = 240, 56%), 78% of respondents reported more than one sleep benefit, although ability to fall asleep was the most commonly cited benefit of use (endorsed by 82% of these respondents). Among those who also had a THC/CBD ratio preference, a significantly higher proportion of high THC-predominant formulation users experienced improvement in ability to fall asleep, and pain that interferes with sleep ($P = 0.001$ and $P = 0.005$, respectively) (Table 3). There were no significant associations between THC/CBD ratio preference and PROMIS pain intensity or sleep disturbance scores; however, in Tukey post-hoc analyses, PROMIS pain interference scores were significantly lower in respondents who preferred pure CBD or CBD-predominant formulations, as compared to the high THC/high CBD group (-4.71 ± 1.56, $p = 0.02$). Similarly, those who reported using high THC/high CBD formulations demonstrated the worst average PROMIS scores for anxiety, fatigue, and cognitive abilities. Centralized pain scores were significantly higher for those who used high

Table 2. Cannabinoid use characteristics

In the past year, have you used cannabis/cannabis products?	
Yes – recreational use	41 (3.4%)
Yes – medical use	273 (22.4%)
Yes – combination of recreation + medical	113 (9.3%)
No	600 (49.3%)
Missing data	190 (15.6%)
For N = 427 who reported using cannabis in the past year:	
Are you currently using cannabis/cannabis products?	
Yes	254 (59.5%)
No	171 (40.1%)
Missing data	2 (0.5%)
For N = 427 who responded using cannabis in the past year, either recreationally or for medical reasons:	
Who helped you to select the type of cannabis product you currently use?	
None/no one	106 (24.8%)
Cannabis dispensary staff	141 (33.0%)
Marijuana industrial/commercial activities	6 (1.4%)
Marijuana caregiver	11 (2.6%)
Family member	49 (11.5%)
Friend	69 (16.2%)
Peer with MS	7 (1.6%)
MS healthcare provider	4 (0.9%)
Other	29 (6.8%)
N	422
Missing data	5 (1.2%)
For N = 386 who used cannabis for medical reasons in the past year (including combination w/recreational):	
What influenced your decision to try cannabis/cannabis products for medical reasons?	
Independent research	248 (64.3%)[a]
Family member	83 (21.5%)
Friend	98 (25.6%)
Peer with MS	104 (26.9%)
MS healthcare provider	70 (18.1%)
Other	42 (10.9%)
For N = 427 who reported using cannabis in the past year:	
In the past year, how frequently have you used cannabis/cannabis products?	
>3 times/day	28 (6.6%)
2–3 times/day	70 (16.4%)
1 time/day	84 (19.7%)
3–5 times/week	62 (14.5%)
1 time/week	29 (6.8%)
1–2 times/month	55 (12.9%)
1–6 times/year	94 (22.0%)
Missing data	5 (1.2%)
For N = 427 who reported using cannabis in the past year:	
Do you prefer a certain ratio of THC to CBD?	
Yes	188 (44.0%)
No	60 (14.1%)
Don't know	177 (41.5%)
Missing data	2 (0.5%)
For N = 188 who had a THC:CBD ratio preference:	
What ratio do you prefer?	

(continued)

Table 2. Continued.

High THC: low CBD	18 (9.6%)
High THC: high CBD	36 (19.2%)
Low THC: high CBD	76 (40.4%)
Low THC: low CBD	14 (7.5%)
Only THC	3 (1.6%)
Only CBD	33 (17.6%)
Not sure	7 (3.7%)
Other	1 (0.5%)
For N = 427 who reported using cannabinoids in the past year:	
What is your preferred method of use?	
Smoking/combustion	93 (21.8%)
Vape	62 (14.5%)
Edibles	114 (26.7%)
Topical/lotion/patch	55 (12.9%)
Capsule	30 (7.0%)
Other	70 (16.4%)
Missing data	3 (0.7%)
For N = 427 who reported using cannabis in the past year:	
How would you characterize the impact of cannabis/cannabis products on your MS symptoms?	
Absolutely beneficial	154 (36.1%)
Some benefit	174 (40.8%)
No effect	50 (11.7%)
Somewhat harmful	4 (0.9%)
Absolutely harmful	1 (0.2%)
Both beneficial and harmful	12 (2.8%)
Don't know	30 (7.0%)
Missing data	2 (0.5%)
For N = 427 who responded using cannabis in the past year, either recreationally or for medical reasons:	
Impact of cannabis on MS symptoms (0 = none; 10 = extreme of complete relief)	
Pain	
Mean (SD)	6.3 (2.2)
Median (IQR)	7 (5, 8)
N (%) who rated benefit from cannabis for this symptom	297(70%)
Sleep concerns	
Mean (SD)	7.5 (2.2)
Median (IQR)	8 (6, 9)
N (%) who rated benefit from cannabis for this symptom	240 (56%)
Spasticity / Muscle tightness	
Mean (SD)	6.5 (2.4)
Median (IQR)	7 (5, 8)
N (%) who rated benefit from cannabis for this symptom	210 (49%)
Anxiety	
Mean (SD)	7.3 (1.9)
Median (IQR)	8 (6, 9)
N (%) who rated benefit from cannabis for this symptom	160 (37%)
Fatigue	
Mean (SD)	6.1 (2.4)
Median (IQR)	7 (5, 8)
N (%) who rated benefit from cannabis for this symptom	68 (16%)
Tremor	
Mean (SD)	7.5 (2.0)

(continued)

Table 2. Continued.

Median (IQR)	8 (7, 9)
N (%) who rated benefit from cannabis for this symptom	43 (10%)
Sexual dysfunction	
Mean (SD)	8.0 (2.4)
Median (IQR)	8.5 (8, 10)
N (%) who rated benefit from cannabis for this symptom	32 (7%)
Attention problems	
Mean (SD)	7.7 (1.5)
Median (IQR)	8 (7, 9)
N (%) who rated benefit from cannabis for this symptom	31 (7%)
MS relapses	
Mean (SD)	7.8 (2.2)
Median (IQR)	8 (7, 9)
N (%) who rated benefit from cannabis for this symptom	22 (5%)
Memory impairment	
Mean (SD)	7.5 (2.2)
Median (IQR)	8 (7, 8)
N (%) who rated benefit from cannabis for this symptom	17 (4%)
Bowel/bladder problems	
Mean (SD)	6.7 (3.2)
Median (IQR)	8 (5, 9)
N (%) who rated benefit from cannabis for this symptom	18 (4%)
Vision difficulties	
Mean (SD)	6.4 (2.0)
Median (IQR)	7 (6, 8)
N (%) who rated benefit from cannabis for this symptom	9 (2%)
For N = 240 who indicated that cannabis can help with sleep:	
Which sleep problems are improved with cannabis/cannabis products? N (%)[a]	
Ability to fall asleep	197 (82.1%)
Ability to stay asleep	143 (59.6%)
More restful or refreshing sleep	89 (37.1%)
Relives pain that interferes with sleep	140 (58.3%)
Other	4 (1.7%)
For N = 427 who reported using cannabis in the past year	
Side effects experienced from using cannabis/cannabis products	
None	236 (55.3%)
Slowed thinking	72 (16.9%)
Weight gain	23 (5.4%)
Decreased attention/concentration	43 (10.1%)
Fatigue	36 (8.4%)
Sleepiness	102 (23.9%)
Anxiety	20 (4.7%)
Hallucinations	3 (0.7%)
Stomach problems/pain	7 (1.6%)
Headache	10 (2.3%)
Chills	2 (0.5%)
Memory problems	25 (5.9%)
Sweating	4 (0.9%)

[a]Respondents instructed to tick all that apply.

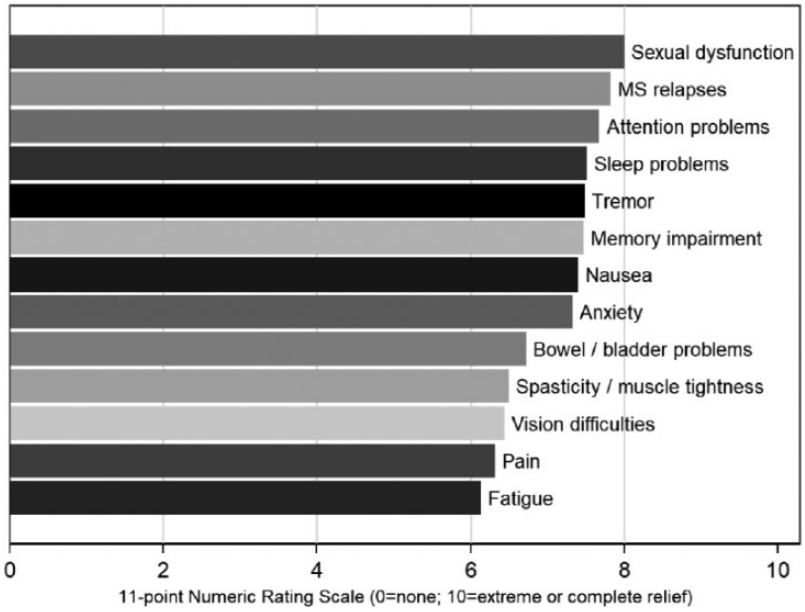

Figure 1. Mean impact of cannabinoid use on MS symptoms (numeric rating scales).

THC/high CBD formulations (Table 3). Mean painDETECT (neuropathic pain) scores were lowest among THC monotherapy/predominant users.

Discussion

These national survey data highlight the rising prevalence of cannabinoid use in Americans with MS, and, among users, an abiding perception of benefit for multiple chronic symptoms. Our findings also demonstrate a growing discrepancy between cannabinoid utilization and clinical guidance regarding use, underscoring a growing need to determine if and how cannabinoids can be more effectively leveraged to treat some of the most disabling MS symptoms that currently lack high quality interventions, and a need to enhance more open educational discussions between providers and patients to optimize cannabinoid use.

Respondents who utilized cannabinoids endorsed benefits for a remarkably wide range of symptoms, beyond pain. For example, perceived benefits of cannabinoids for sleep complaints, per numeric rating scales, exceeded the magnitude of perceived benefits on pain and subjective spasticity – symptoms most commonly recognized as responsive to the effects of cannabinoids.[10,11] Our findings also suggest differential benefits for specific insomnia types, with greatest benefits reported for sleep initiation. Over half of respondents also reported that cannabinoids helped with pain interference in sleep, which corresponded with the high correlation between NRS impact scores for sleep and pain relief with cannabinoids (correlation coefficient 0.65, $p < 0.0001$). Given the bidirectional relationship between sleep and pain in MS and other populations,[6,25,26] and responses indicating a significant benefit in pain-related insomnia symptoms, this particular palliative effect in MS deserves further exploration.

The perceived differential effects of CBD and THC on sleep, pain, and other MS symptoms in our study also deserve comment. Although the majority of the sample preferred low THC/high CBD ratio preparations (Table 3), a higher proportion of respondents who preferred high THC formulations endorsed benefits in specific sleep symptoms. This finding should be interpreted with caution, given the low number of THC-predominant users, but raises questions about potential disparate effects of individual cannabinoids on sleep. Indeed, the utility of various THC:CBD ratios for MS-related pain and other symptoms are not well understood. Both THC and CBD may have different potential benefits for pain and sleep in other populations, or differential effects based on dose,[27] yet the majority of research to date for these symptoms in MS has focused on a 1:1 or 2:1 combination of THC/CBD (Nabiximol/Sativa, Cannador),[13,28–30] with fewer studies dedicated to THC or CBD monotherapy. Interestingly, in a prior study of persons without MS who had insomnia, administration of a conventionally high dose of CBD (160 mg/day) was shown to increase total sleep

Table 3. CBD/THC ratio preference characteristics (for n = 180 who endorsed a preference).

	Low THC: Low CBD N = 14	High THC: High CBD N = 36	CBD monotherapy or predominant therapy N = 109	THC monotherapy or predominant therapyN = 21	p-value
Reported sleep benefits					
Ability to fall asleep	6 (43%)	27 (75%)	46 (42%)	15 (71%)	0.001
Ability to stay asleep	2 (14%)	19 (53%)	39 (36%)	8 (38%)	0.08
More restful/refreshing sleep	4 (29%)	12 (33%)	24 (22%)	2 (10%)	0.20
Relieves pain that interferes with sleep	4 (29%)	25 (69%)	41 (38%)	9 (43%)	0.005
PROMIS short-form T-score Mean (SD)					
Pain intensity	49.6 (7.7)	52.6 (6.3)	49.2 (7.1)	48.4 (9.1)	0.09
Pain interference	59.1 (9.0)	63.2 (5.8)	58.5 (8.4)	58.1 (9.3)	0.02
Depression	55.7 (10.8)	58.6 (8.9)	54.7 (8.3)	56.0 (10.5)	0.14
Anxiety	56.9 (7.1)	58.8 (8.2)	53.7 (9.1)	55.3 (7.4)	0.02
Fatigue	60.5 (9.3)	63.9 (7.0)	58.3 (8.7)	59.7 (8.9)	0.009
Sleep disturbance	52.1 (3.9)	54.3 (4.8)	53.2 (4.7)	54.1 (4.8)	0.43
Cognitive abilities	46.7 (9.0)	40.5 (8.0)	44.3 (7.0)	44.4 (9.1)	0.03
Pain characteristics					
Centralized pain FM survey score, mean (SD)	12 (5)	15 (5)	12 (6)	13 (6)	0.04
Neuropathic pain pain DETECT score, mean (SD)	20 (9)	19 (7)	16 (8)	14 (9)	0.02

time and decrease arousals during the night.[27] Conversely, low-dose CBD has been associated with increased wakefulness in some non-MS samples.[31] Additional studies are necessary to determine if and how formulations should differ depending on underlying pain mechanisms, or sleep disturbances, and other clinical phenotypes within an individual.

Although dosing information regarding CBD and THC are not available from these survey data, this prior work also invites speculation regarding differential effects of CBD dosing on fatigue – a common consequence of sleep disorders in MS,[3,4] and a symptom that was reported to be improved by cannabinoids in 16% of our sample. Indeed, although benefits were endorsed most frequently for pain, sleep, and spasticity (endorsed by 80%, 56% and 49% of respondents, respectively), at least some proportion of those who used cannabinoids endorsed benefit for each symptom that was queried. Furthermore, median NRS benefit scores were strong, even among symptoms that responded to cannabinoids for only in a minority of cannabinoid users. Future cannabinoid MS research may benefit from studies that qualitatively assess symptoms more broadly.

Although a substantial proportion (41%) of our sample reported uncertainty or ambivalence regarding preferred cannabinoid formulation, a commensurate proportion expressed a clear preference regarding THC/CBD ratio. The latter is particularly notable, given the reported lack of expert guidance surrounding cannabinoid use. Interestingly, the overwhelming majority of respondents expressed a desire to receive more guidance from healthcare providers on cannabis use, yet fewer than 1% received information from their provider about the type of cannabinoid product that they used, highlighting an important potential gap in MS care. Although the NMSS "*supports the ability of people living with MS to make informed choices about their treatments with their MS health care providers, including the use of medical cannabis*" (https://www.nationalmssociety.org/Treating-MS/Complementary-Alternative-Medicines/Marijuana/Marijuana-FAQs), our findings suggest that communication between patients and providers regarding cannabinoid use has not paralleled the rise in consumer use. A similarly low proportion of patient/provider engagement was noted in a previous study of PwMS in 2014,[32] yet the prevalence of marijuana use was also reported to be lower at the time the study was conducted.

Reasons for the discrepancy, whether patient- or provider-driven, have not been adequately explored, but could relate to insufficient clinically-actionable evidence regarding the utility of cannabinoid for MS symptom management. We considered the possibility that difference in state-by-state legislation might have impacted our findings, but a low number of respondents in some of these states precluded a definitive evaluation of whether legality of cannabinoids influenced these findings.

Similar to our sample, demographic profiles of samples from previous cross-sectional survey studies of cannabis use in PwMS were predominantly female, Caucasian, and RRMS subtype.[12,32,33] Our findings also show concordance with earlier studies regarding an association between cannabis use and higher level of disability.[32] Such findings could signal a typical profile of cannabinoid users; however, homogeneity across prior studies suggests a need for more research focused on minority or underserved groups. Although the prevalence of lifetime (ever) cannabinoid use has been higher in some studies,[12,32,34] the prevalence of *recent or current* use in our sample (42% and 25%, respectively) exceeds current/recent use estimates previously reported in other North American samples.[12,32–34] While definitions regarding "recent" use, study settings, and regions of interest differ between studies, our data suggest an upward trend in cannabinoid use among Americans with MS.

Strengths of this study include use of a large national sample that encompassed a wide geographical distribution, and inclusion of states in which cannabinoids are still illegal for medical use. Assistance from the NMSS for identification of respondents, and survey items that assessed diagnostic workup and current DMT use enhanced reliability of respondent diagnosis. Inclusion of pain phenotype and a more in-depth examination of insomnia symptoms, in the context of specific THC/CBD ratios, builds upon existing evidence regarding patient-reported benefits, and promotes the generation of new hypotheses regarding the relationship between cannabinoids, sleep, and pain.

Some limitations should also be acknowledged. A possibility exists that response bias could have led to overstatement of treatment benefits; however, given that the primary purpose of this parent survey was to characterize MS-related pain (which was explained to potential respondents before the survey) the likelihood that the survey selectively targeted cannabinoid users was plausibly reduced. Although evaluation of THC/CBD ratios provides new data regarding differential treatment effect and utilization patterns, given the unregulated status of these products even in states where cannabis is medically or recreationally legal, respondents may not be fully aware of the composition of the reported cannabinoid products. At present, consumer knowledge of cannabinoid composition heavily hinges on transparency of growers and cannabinoid dispensary sales staff.

Many Americans with MS use cannabinoids, and CBD-predominant products in particular, to self-manage a wide range of symptoms. These findings highlight crucial gaps between community use and clinical care, and illustrate an immediate need for prospective, mechanistic studies focused on the effects of cannabinoids for chronic MS symptoms, as well as interactions between MS symptoms.

Authors' Note

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