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Symptom severity is a major determinant of cannabis-based products use among people with multiple sclerosis

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Abstract

Aims and Objectives: We aimed to identify correlates of cannabinoid-based products (CBP) use in patients with multiple sclerosis (MS) in France and Spain.

Background: MS is responsible for a wide range of symptoms, including pain. Access to CBP differs according to local legislation. The French context is more restrictive than the Spanish one, and no data regarding cannabis use among MS patients has yet been published. Characterizing MS patients who use CBP constitutes a first step toward identifying persons most likely to benefit from them.

Design: An online cross-sectional survey was submitted to MS patients who were members of a social network for people living with chronic diseases and were living in France or Spain.

Methods: Two study outcomes measured therapeutic CBP use and daily therapeutic CBP use. Seemingly unrelated bivariate probit regression models were used to test for associations between the outcomes and patients' characteristics while accounting for country-related differences. STROBE guidelines were followed in reporting this study.

Results: Among 641 study participants (70% from France), the prevalence of CBP use was similar in both countries (23.3% in France vs. 20.1% in Spain). MS-related disability was associated with both outcomes, with a gradient observed between different degrees of disability. MS-related pain level was associated with CBP use only.

Conclusions: CBP use is common in MS patients from both countries. The more severe the MS, the more participants turned to CBP to alleviate their symptoms. Easier access to CBP should be ensured for MS patients in need of relief, especially from pain.

Tangui Barré and Damien Testa equally contributed to this work.

Lise Radoszycki and Camelia Protopopescu equally contributed to this work.

There is a statistician on the author team: C. Protopopescu.

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Relevance to clinical practice: This study highlights the characteristics of MS patients using CBP. Such practices should be discussed by healthcare professional with MS patients.

KEYWORDS

cannabis, multiple sclerosis, patient-reported outcomes, symptom management

1 | INTRODUCTION

Multiple sclerosis (MS) is an incurable immune-mediated inflammatory disease of the central nervous system whose underlying causes are unclear. It is responsible for chronic neurological disability (Dobson & Giovannoni, 2019). Global prevalence in 2015 was estimated at more than two million people (Feigin et al., 2017), and is on the rise (Walton et al., 2020). MS is generally diagnosed during young adulthood or middle age (Gilmour et al., 2018) and is more frequent in women (Dobson & Giovannoni, 2019).

The phenotypes commonly used to characterise MS are clinically isolated syndrome, relapsing–remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS; Lublin et al., 2020; Thompson et al., 2018). RRMS is characterised by relapses—acute or subacute episodes of new or increasing neurologic dysfunction—followed by full or partial recovery (Lublin et al., 2014). Progressive MS is characterised by steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (Lublin et al., 2014). More specifically, PPMS is characterised by a progressive state of MS from onset, while in SPMS, the progressive state follows one or more relapses (Lublin et al., 2014).

Multiple sclerosis is responsible for a wide range of potentially debilitating symptoms including spasticity, pain, fatigue, depression, impairment of cognitive functions, reduced mobility and decreased bladder function. Symptoms tend to worsen with time (Kister et al., 2013, 2020). Despite advances in treatment, there is still no cure (Dobson & Giovannoni, 2019; McGinley et al., 2021). Disease-modifying therapies and symptomatic therapies are also often used to treat its symptoms (Dobson & Giovannoni, 2019).

The medical use of cannabinoids to reduce MS symptoms is still controversial. Research evidence for the potential benefits of cannabinoids on MS-related pain is not as strong as for spasticity (Nielsen et al., 2018; Rice & Cameron, 2017). Nabiximols—an oromucosal spray with a balanced mixture of tetrahydrocannabinol (THC) and cannabidiol (CBD)—is approved by health regulatory authorities in several countries for adult patients with moderate to severe MS-related spasticity who do not respond adequately to other anti-spasticity medication (Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2014; Electronic Medicines Compendium, 2020). A number of countries, including Canada, also authorise its use for MS-associated neuropathic pain (Abuhassira et al., 2018). However, this is not the case in France or Spain. Access to cannabis and to cannabinoid-based products (CBP), whether for

What does this paper contribute to the wider global clinical community?

- This study reveals that French and Spanish multiple sclerosis patients commonly use cannabis-based products.
- The more severe the multiple sclerosis, the more participants turned to cannabis-based products to alleviate their symptoms.

therapeutic or recreational purposes, varies according to local legislation. In France, while cannabis consumption is very common, it is criminalised by law. Furthermore, despite nabiximols being the only legal cannabinoid-based medical drug in the country, it is unavailable because of failures in price negotiations between its producer and French health authorities. Since March 2021, a national experimental test has been implemented in France to assess the relevance and feasibility of making medical cannabis available, with 3000 participants expected. Among the conditions for enrolment are neuropathic pain refractory to accessible therapies and painful refractory MS-related spasticity (Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2021). Conversely, in Spain, cannabis use is decriminalised. Social clubs are organised for cannabis production and distribution (Belackova & Wilkins, 2018). Just as in France, nabiximols is the country's only legal cannabinoid-based medical drug available (nabilone and dronabinol are only authorised for "exceptional cases of MS" in Spain (Gorospa Elezcano, 2020)). It can only be dispensed in hospital pharmacies. Therefore, depending on the national legal context (i.e. France vs. Spain), people with MS may self-medicate with cannabis and/or cannabinoid-based drugs, or use them under medical supervision to alleviate their symptoms (Gupta et al., 2019; Gustavsen et al., 2019; Weinkle et al., 2019). Despite these legal and medical possibilities for cannabis use, no guidelines exist in either country for physicians who wish to counsel their patients with MS about the putative therapeutic use of cannabis (Calcaterra et al., 2020). Characterising CBP use in MS patients constitutes a first step in understanding the potential therapeutic benefits of cannabinoids, and therefore in identifying patients most likely to benefit from them.

Moreover, as cannabis-based self-medication does not come without risks (e.g. side effects and drug–drug interactions (Brown & Winterstein, 2019)), identifying patients most likely to use CBP,

as well as their motivations to do so, may help healthcare providers initiate discussion with them on this issue, and provide proper guidelines and harm reduction counselling. Due to the sensitive nature of issues related to the use of (formerly) illicit substances, some patients may be reluctant to talk about their consumptions with their healthcare providers, especially physicians, or may underreport their use, by fear of stigmatisation (Hulaihel et al., 2022; Nayak et al., 2022; Troup et al., 2022). They may more openly talk about this with nurses, as the latter may have better listening skills, be less prone to top-down decision making, and have more positive attitude toward CBP (and thus lower stigma) compared to physicians (HaGani et al., 2022; Melnikov et al., 2021; Ubel et al., 2017). Providing detailed information to nurses about CBP use in MS patients is thus important to help them contextualise this issue and to guide them in their routine interactions with MS patients.

This study aimed to identify correlates of CBP use in patients with MS in France and Spain.

2 | METHODS

2.1 | Study design and participants

Carecity is a social network for people living with chronic conditions, created in 2011 to provide high quality medical information to an online patient community and to help patients and caregivers find support and share their experiences about chronic diseases via online forums. This community has more than 500000 members from six different countries and generates real-world patient insights through online surveys (Carecity, 2019).

Carecity members living with MS (as self-reported), aged 18 years and older, and living in France or Spain were eligible for inclusion in this study. Participants voluntarily enrolled from April to July 2019, provided signed informed consent, and responded to a confidential web-based survey. No financial incentive was provided to participate in the survey.

2.2 | Questionnaire and data collection

Participants completed a self-administered online questionnaire comprising one open and 30 closed questions exploring sociodemographic characteristics, clinical and psychosocial aspects of MS, and CBP use patterns in the context of coping with MS.

The sociodemographic characteristics collected included gender, age, country of residence, city size and highest educational level attained. With regard to clinical and psychosocial aspects of MS, we collected data on the type of MS (RRMS, SPMS, PPMS, unknown), presence of MS-related spasticity (yes, no, unknown), time since diagnosis, self-perceived global health level (visual analogue scale from 0 indicating the worst imaginable health state, to 10 indicating the best imaginable health state; Atkinson & Lennox, 2006), and

MS-related pain level (visual analogue scale from 0, indicating no pain to 10, indicating extreme pain; Karcioğlu et al., 2018). The severity of MS-related disability was estimated by a neurologic and walking impairment score, adapted from the Expanded Disability Status Scale (EDSS). As clinical evaluation was not available, 11 pre-determined items were proposed to obtain a self-assessed EDSS level for each participant (see Table S2 for the complete list). The score quantified the level of disability from 0 to 10, based on a neurologic evaluation of eight functional systems and walking impairment; a higher score represented a higher level of disability (Kurtzke, 1983).

The frequency of CBP use was collected for those who declared using it for therapeutic purposes (in any form, including herb and cannabinoid-based forms, whether plant-derived or synthetically manufactured) to alleviate their MS symptoms. We also collected data on the type of CBP they used, and where they bought products. To collect these two data, participants could choose one or more options from a pre-defined list.

2.3 | Study outcomes

Two outcomes were defined, both based on therapeutic CBP use frequency: CBP use (vs. no use) and daily CBP use (vs. no use or less than daily use). In both outcomes, the term CBP encompassed all cannabis and/or cannabinoid-based products (such as herb, nabiximols or CBD-rich oil).

2.4 | Statistical analyses

The characteristics of study participants were described using numbers and percentages for categorical variables and means (standard deviations) for continuous ones. They were described globally, according to country of residence (i.e. France or Spain) and according to CBP use frequency. Users' patterns of CBP use were also described.

For each outcome, we used a seemingly unrelated bivariate probit regression model, which allowed us to account for the potential bias related to the differences between participants' characteristics according to their country of residence. This approach was based on two simultaneous equations with correlated error terms and robust standard errors (Huber/White/sandwich estimator of the variance), estimated by the Stata "biprobit" command (Greene, 2017). In the first equation, the factors associated with the country of residence were identified using a multivariable probit regression model. The second equation, with each of the study outcomes as the dependent variable, was estimated by maximum likelihood together with the previously identified first equation. This second equation was adjusted for the country of residence in all univariable and multivariable analyses, the former effectively being bivariable analyses that included each of the explanatory variables plus the country variable.

A similar (univariable/multivariable) selection procedure was used for the two equations of the seemingly unrelated bivariate probit model. The threshold for identifying eligible variables in the

univariable analyses was p -value < 0.20 (Wald test). A backward selection procedure was then used to obtain the final multivariable models, with the p -value threshold for statistical significance set at 0.05. A positive/negative coefficient in the probit regression models indicates a direct/inverse association between the corresponding explanatory variable and the outcome.

The following explanatory variables were tested in the models: gender, city size (recoded into < 1000 ; 10,000–100,000; and $> 100,000$ inhabitants), educational level (recoded into $>$ vs. \leq upper secondary school certificate), time since diagnosis, age at diagnosis, MS-related spasticity, type of MS, MS-related disability (none or minimal (score 0–2), moderate or substantial (score 3–7), and total disability (score 8–10)), self-perceived global health level and MS-related pain level.

The study was conducted according to the “strengthening the reporting of observational studies in epidemiology” (STROBE) statement for cross-sectional studies (see Table S1). Stata/SE 16.1 software (StataCorp LP) was used for all analyses.

2.5 | Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. According to the French law and thanks to the anonymity of data, no approval from ethics committee was needed. Informed written consent was obtained from all participants included in the study.

3 | RESULTS

3.1 | Study population characteristics

Our study population included 641 Carenity members, 447 (69.7%) of whom lived in France and 194 (30.3%) in Spain. The study population comprised mainly women (72.7%); the mean age was 47.1 years; most of them (73.2%) experienced MS-related spasticity; and 54.5% and 16.8% underwent moderate or substantial disability and total disability, respectively (Table 1). According to the univariable probit regression analyses, participants from Spain were less likely than those in France to live in cities with < 1000 inhabitants. Instead, they were more likely to (i) have RRMS, (ii) not know whether they had spasticity, (iii) suffer from less severe MS-related disability, (iv) have been diagnosed for a shorter time, (v) have been diagnosed at a younger age, (vi) have a higher self-reported global health level and (vii) have a lower self-reported MS-related pain level (Table 1). After multivariable adjustment, differences remained for city size, type of MS, MS-related disability, time since diagnosis and age at diagnosis.

Less than a quarter (22.3%) of all the survey participants used CBP to alleviate their MS symptoms, and 70.0% of users used them daily (Figure 1). There was no between-country difference in the two measured frequencies of CBP use (CBP use prevalence was

23.3% in France vs. 20.1% in Spain, χ^2 test p -value = 0.377; daily CBP use prevalence was 16.1% in France vs. 14.4% in Spain, $p = 0.591$; Figure 1).

Patterns of therapeutic CBP use revealed between-country differences for most variables, with noticeable exceptions being the use of herb/resin and purchasing on the street or from relatives (Table 2).

3.2 | Correlates of therapeutic CBP use in MS patients

According to the results from the bivariate probit models, in univariable analyses, the factors associated with therapeutic CBP use (yes/no) were male gender, MS-related disability and MS-related pain level (Table 3). After multivariable adjustment, male gender (probit coefficient [95% confidence interval (CI)]: 0.34 [0.09;0.58]), MS-related disability—with a gradient between the categories “moderate or substantial disability” (0.36 [0.05;0.67]) and “total disability” (0.51 [0.13;0.88]) versus “no or minimal disability”—and MS-related pain level (0.04 [0.00;0.09] per one-point increase on a 10-point visual analogue scale), were all independently associated with CBP use (Table 3).

In univariable analyses, daily CBP use (vs. no use or less than daily use) was associated with SPMS (vs. the reference RRMS), MS-related disability and MS-related spasticity (Table 4). After multivariable adjustment, this outcome was only associated with MS-related disability, with a similar gradient between the categories to that described above: coefficient [95% CI]: 0.40 [0.06;0.73] and 0.60 [0.20;0.99] for “moderate or substantial disability” and “total disability”, respectively, versus “no or minimal disability” (Table 4).

4 | DISCUSSION

This real-world international study based on patient-reported outcomes from a web-based survey showed that patients with MS who had higher levels of related disability and those with higher levels of pain were more likely to use CBP for therapeutic purposes. Moreover, despite different legislation contexts, including the difficulty for French patients to obtain cannabinoid-based pharmaceutical products, the prevalence of CBP use was similar in patients from both Spain and France, and most users in both countries consumed CBP daily. Given that the French participants generally had a more advanced stage of the disease (i.e. more progressive forms of MS, longer time since diagnosis and increased MS-related disability) than their Spanish counterparts, the similar prevalences of CBP use in both countries suggests that people living with MS in France use CBP for therapeutic purposes as a last resort at an advanced stage of their disease.

This is the very first time that CBP use is documented among people living with MS in the sociocultural and legislative context of France. Previous studies focused on cannabis, while we provided

TABLE 1 Characteristics of the study participants according to country of residence and factors associated with living in Spain (probit regression, univariable and multivariable analyses, Carenity survey, $n = 641$).

	Total ($n = 641$)		France ($n = 447$)		Spain ($n = 194$)		Univariable analyses		Multivariable analysis	
	No. of participants (%) or mean (SD)		No. of participants (%) or mean (SD)		No. of participants (%) or mean (SD)		Coeff [95% CI]	p-value	aCoeff [95% CI]	p-value
Gender										
Female (ref.)	466 (72.7)		331 (74.0)		135 (69.6)		1			
Male	175 (27.3)		116 (26.0)		59 (30.4)		0.13 [-0.09;0.36]	.246		
Age (years) ^a	47.1 (11.1)		49.1 (11.5)		42.5 (8.7)		-0.04 [-0.05;-0.03]	<10 ⁻³		
Town/city size (no. of inhabitants)								<10 ⁻³		<10 ⁻³
<1000 (ref.)	254 (39.6)		208 (46.5)		46 (23.7)		1		1	
10,000-100,000	226 (35.3)		154 (34.5)		72 (37.1)		0.44 [0.20;0.69]	.001	0.45 [0.19;0.71]	.001
>100,000	161 (25.1)		85 (19.0)		76 (39.2)		0.84 [0.58;1.11]	<10 ⁻³	0.85 [0.57;1.13]	<10 ⁻³
Educational level										
≤upper secondary school certificate (ref.)	330 (51.5)		239 (53.5)		91 (46.9)		1			
>upper secondary school certificate	311 (48.5)		208 (46.5)		103 (53.1)		0.15 [-0.05;0.36]	.127		
Time since diagnosis (years)	12.4 (9.2)		13.1 (9.7)		10.9 (7.6)		-0.02 [-0.03;-0.01]	.002	-0.02 [-0.03;-0.00]	.019
Age at diagnosis (years)	34.7 (10.3)		36.0 (10.7)		31.6 (8.5)		-0.03 [-0.04;-0.02]	<10 ⁻³	-0.02 [-0.04;-0.01]	<10 ⁻³
MS-related spasticity								.037		
Yes (ref.)	469 (73.2)		340 (76.1)		129 (66.5)		1			
No	98 (15.3)		63 (14.1)		35 (18.0)		0.23 [-0.05;0.51]	.107		
Unknown	74 (11.5)		44 (9.8)		30 (15.5)		0.36 [0.05;0.67]	.025		
Type of MS ^b								<10 ⁻³		.004
RRMS (ref.)	365 (56.9)		221 (49.4)		144 (74.2)		1		1	
PPMS	95 (14.8)		80 (17.9)		15 (7.7)		-0.74 [-1.07;-0.40]	<10 ⁻³	-0.52 [-0.90;-0.14]	.007
SPMS	135 (21.1)		114 (25.5)		21 (10.8)		-0.75 [-1.03;-0.46]	<10 ⁻³	-0.59 [-0.95;-0.23]	.001
Unknown	46 (7.2)		32 (7.2)		14 (7.2)		-0.24 [-0.65;0.16]	.233	-0.12 [-0.52;0.28]	.552
Disease disability score (adapted from the EDSS) ^c								<10 ⁻³		.007
No or minimal disability (ref.)	184 (28.7)		97 (21.7)		87 (44.8)		1		1	
Moderate or substantial disability	349 (54.5)		268 (60.0)		81 (41.8)		-0.66 [-0.90;-0.43]	<10 ⁻³	-0.33 [-0.59;-0.07]	.013
Total disability	108 (16.8)		82 (18.3)		26 (13.4)		-0.64 [-0.95;-0.32]	<10 ⁻³	0.06 [-0.34;0.47]	.759

TABLE 1 (Continued)

	Total (n = 641)		France (n = 447)		Spain (n = 194)		Univariable analyses		Multivariable analysis	
	No. of participants (%) or mean (SD)		No. of participants (%) or mean (SD)		No. of participants (%) or mean (SD)		Coeff [95% CI]	p-value	aCoeff [95% CI]	p-value
Global health level (VAS) ^d	5.9 (2.3)		5.7 (2.2)		6.3 (2.5)		0.07 [0.03;0.12]	.002		
MS-related level of pain (VAS) ^e	4.2 (2.7)		4.3 (2.6)		3.8 (3.0)		-0.04 [-0.08;-0.00]	.035		
Intercept									0.48 [-0.06;1.01]	.081

Abbreviations: aCoeff, adjusted probit coefficient; CI, confidence interval; Coeff, probit coefficient; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; ref., reference; SD, standard deviation; VAS, visual analogue scale.

^aStatistics for age are provided for descriptive purposes only. This variable was not entered in the models.

^bType of MS: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), unknown.

^cDisease severity score (adapted from the EDSS): no or minimal disability (0–2), moderate or substantial disability (3–7), total disability (8–10).

^dGlobal health level (VAS): from 0 (the worst imaginable health state) to 10 (the best imaginable health state).

^eMS-related pain level (VAS): from 0 (no pain) to 10 (extreme pain).

data for CBP as a whole. This original international study revealed that despite CBD or cannabis-based products being partly available, herb/resin remain the most commonly used products.

Despite the potential barriers to CBP access, the prevalence of use we found here would suggest that patients use cannabis or CBP because they alleviate their symptoms, especially neurologic/walking impairments, and pain. Nabiximols is generally approved for spasticity treatment but not for MS-related pain (Electronic Medicines Compendium, 2020). In countries where medical cannabis is approved, chronic pain is one of the most common conditions for its prescription (Boehnke et al., 2019; Schmidt-Wolf & Cremer-Schaeffer, 2021). In their systematic review, Nielsen et al. (2018) concluded that “recent high quality reviews supported the clinical use of cannabinoids for spasticity and pain in MS”. With regard to pain, they reported one low-quality randomised controlled trial which highlighted positive effects for smoked cannabis, and 15 studies of varying quality which highlighted mixed effects for products based on a THC/CBD mixture. The responsiveness to the ataxic, antinociceptive and hypothermic effects of THC seems to be partially genetically determined (Parks et al., 2020), and may therefore partly explain the mixed results cited above.

Our results regarding pain are consistent with patient-reported outcomes from MS patients using cannabis for therapeutic reasons in different countries (Guarnaccia et al., 2021; Martínez-Rodríguez et al., 2008; Page & Verhoef, 2006). They reflect results from the French sub-sample of the present survey, in which 75% of CBP users reported positive CBP-related change in pain (Barré et al., 2022). They also echo previous evidence that cannabis and/or cannabinoids are beneficial in MS-related spasticity and neuropathic pain (Nielsen et al., 2018; Rice & Cameron, 2017). More broadly, MS patient-reported data elsewhere highlighted insomnia, mood disorders, nausea, and bladder problems as other MS-related symptoms which were alleviated by the use of cannabis (Clark et al., 2004; Guarnaccia et al., 2021; Page & Verhoef, 2006).

Our results for the prevalence of “natural” (i.e. non-synthetic) cannabis use—approximately 10% of the study population if we consider that half of those taking CBP used herb/resin-based products—are also consistent (despite being in the lower range) with previous reported cannabis use prevalence of 10%–50% in MS patients (Banwell et al., 2016; Chong et al., 2006; Clark et al., 2004; Gupta et al., 2019; Gustavsen et al., 2019; Martínez-Rodríguez et al., 2008; Ware et al., 2005). Specifically, the prevalence we found for Spain is consistent with that found by Martínez-Rodríguez et al. (2008) (17.1%). The lower values we found for cannabis use may be explained by the sampling process, which may have over-represented MS patients who were more informed about the disease and/or were more health-conscious, as well as those who preferred less harmful (i.e. non-smoked) routes of administration. They may also be explained by the all-encompassing definition used for cannabis in other studies (i.e. where all types of CBP, not only herb or resin, were considered as cannabis).

The association we found between self-reported MS-related pain and disability and CBP use is consistent with previous results

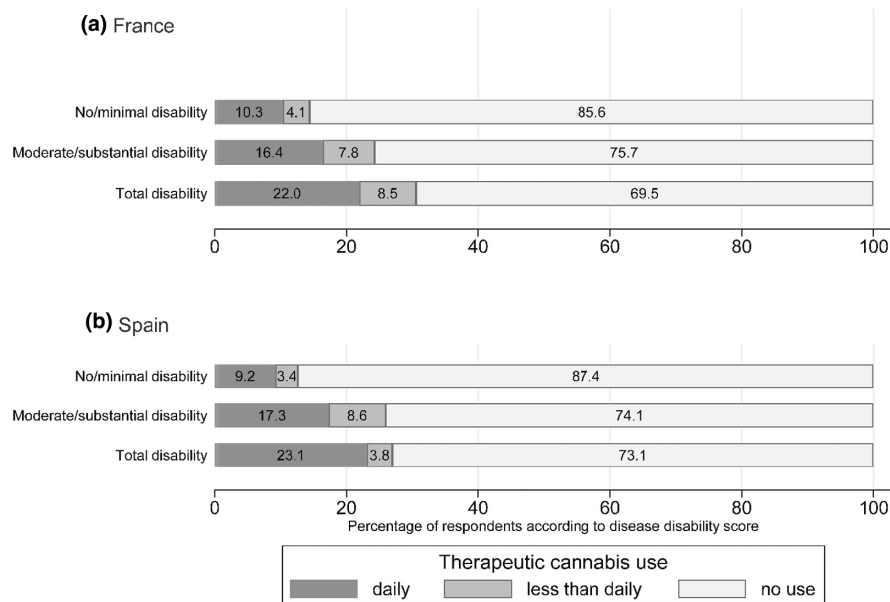


FIGURE 1 Cannabis-based products use in people with multiple sclerosis according to disease disability score as a function of country of residence: (a) France; (b) Spain (Carenity survey, $n = 641$).

	All participants ($n = 143$)	France ($n = 39$)	Spain ($n = 104$)	p -value ^a
	No. of participants (%)	No. of participants (%)	No. of participants (%)	
Cannabis-based product^b				
Nabiximols	19 (13.3)	3 (2.9)	16 (41.0)	$<10^{-3}$
Edible	6 (4.2)	2 (1.9)	4 (10.3)	.047
Vaping	24 (16.8)	24 (23.1)	0 (0.0)	$<10^{-3}$
Pills/capsules	10 (7.0)	10 (9.6)	0 (0.0)	.062
Dried herb/ resin	67 (46.8)	47 (45.2)	20 (51.3)	.516 ^c
Oil	53 (37.1)	48 (46.1)	5 (12.8)	$<10^{-3c}$
Ointment	4 (2.8)	3 (2.9)	1 (2.6)	1.000
Spray	3 (2.1)	0 (0.0)	3 (7.7)	.019
Purchase location^b				
Pharmacy	22 (15.4)	4 (3.8)	18 (46.1)	$<10^{-3}$
Internet	46 (32.2)	43 (41.3)	3 (7.7)	$<10^{-3}$
Bordering country	19 (13.3)	19 (18.3)	0 (0.0)	.002
From relatives	40 (28.0)	29 (27.9)	11 (28.2)	.970 ^c
On the street	26 (18.2)	21 (20.2)	5 (12.8)	.309 ^c

TABLE 2 Patterns of cannabis-based products and purchase location by users according to their country of residence (Carenity survey, $n = 143$).

^aFisher's exact test by default.

^bMultiple responses were possible.

^cChi-squared test.

for Spain (Martínez-Rodríguez et al., 2008) and the UK (Chong et al., 2006). This association also suggests that CBP start to be used as a therapeutic strategy when MS symptoms become unbearable and/or other treatment options have failed to alleviate them. This is in line with the approval of nabiximols by the French and Spanish health authorities for non-respondent patients (i.e. who do not respond adequately to other anti-spasticity medication; Agence

Nationale de Sécurité du Médicament et des Produits de Santé, 2014; Almirall, 2010). Our results indirectly suggest that patients tend to assess for themselves the benefit-risk balance of CBP use, and that the more severe the disability and/or pain, the more likely they are to try using CBP to alleviate symptoms. Among the barriers that patients may have to overcome in this context, we can cite illegality (Banwell et al., 2016), fear of side effects (Pratt et al., 2019; Urits

TABLE 3 Factors associated with cannabis-based products use in people with multiple sclerosis, taking into account differences in participants' characteristics according to country of residence (seemingly unrelated bivariate probit regression, univariable and multivariable analyses, Carenity survey, $n = 641$).

	Total ($n = 641$) No. of participants (%) or mean (SD)	Cannabis-based products use		Univariable analyses ^a		Multivariable analysis ^b	
		No ($n = 498$) No. of participants (%) or mean (SD)	Yes ($n = 143$) No. of participants (%) or mean (SD)	Coeff [95% CI]	p -value	aCoeff [95% CI]	p -value
Country of residence							
France (ref.)	447 (69.7)	343 (68.9)	104 (72.7)	1		1	
Spain	194 (30.3)	155 (31.1)	39 (27.3)	-0.50 [-1.10;0.10]	.100	0.20 [-0.54;0.95]	.589
Gender							
Female (ref.)	466 (72.7)	375 (75.3)	91 (63.6)	1		1	
Male	175 (27.3)	123 (24.7)	52 (36.4)	0.31 [0.07;0.55]	.012	0.34 [0.09;0.58]	.006
Age (years)	47.1 (11.1)	46.9 (11.1)	47.9 (11.3)	-0.00 [-0.02;0.01]	.695		
Town/city size (no. of inhabitants)							
<1000 (ref.)	254 (39.6)	194 (39.0)	60 (42.0)	1			
10,000–100,000	226 (35.3)	176 (35.3)	50 (35.0)	0.04 [-0.23;0.31]	.764		
>100,000	161 (25.1)	128 (25.7)	33 (23.1)	0.08 [-0.29;0.44]	.669		
Educational level							
≤upper secondary school certificate (ref.)	330 (51.5)	260 (52.2)	70 (49.0)	1			
>upper secondary school certificate	311 (48.5)	238 (47.8)	73 (51.1)	0.10 [-0.11;0.31]	.372		
Time since diagnosis (years)	12.4 (9.2)	12.1 (8.9)	13.5 (9.8)	0.01 [-0.01;0.02]	.260		
Age at diagnosis (years)	34.7 (10.3)	34.8 (10.3)	34.4 (10.5)	-0.01 [-0.02;0.00]	.139		
MS-related spasticity related to MS							
Yes (ref.)	469 (73.2)	353 (70.9)	116 (81.1)	1			.052
No	98 (15.3)	86 (17.3)	12 (8.4)	-0.44 [-0.80;-0.08]	.016		
Unknown	74 (11.5)	59 (11.9)	15 (10.5)	-0.12 [-0.47;0.23]	.500		
Type of MS ^c							
RRMS (ref.)	365 (56.9)	288 (57.8)	77 (53.9)	1			
PPMS	95 (14.8)	71 (14.3)	24 (16.8)	0.05 [-0.33;0.43]	.787		
SPMS	135 (21.1)	98 (19.7)	37 (25.9)	0.12 [-0.23;0.47]	.514		
Unknown	46 (7.2)	41 (8.2)	5 (3.5)	-0.46 [-0.96;0.04]	.073		
Disease disability score (adapted from the EDSS) ^d							
No or minimal disability (ref.)	184 (28.7)	159 (31.9)	25 (17.5)	1		1	.024

(Continues)

TABLE 3 (Continued)

	Total (n = 641)	Cannabis-based products use		Univariable analyses ^a	Multivariable analysis ^b		
		No (n = 498)	Yes (n = 143)				
	No. of participants (%) or mean (SD)	No. of participants (%) or mean (SD)	No. of participants (%) or mean (SD)	Coeff [95% CI]	p-value	aCoeff [95% CI]	p-value
Moderate or substantial disability	349 (54.5)	263 (52.8)	86 (60.1)	0.45 [0.14;0.76]	.004	0.36 [0.05;0.67]	.025
Total disability	108 (16.9)	76 (15.3)	32 (22.4)	0.60 [0.23;0.96]	.001	0.51 [0.13;0.88]	.008
Global health level (VAS) ^e	5.9 (2.3)	5.9 (2.3)	5.7 (2.4)	-0.00 [-0.06;0.05]	.866		
MS-related level of pain (VAS) ^f	4.2 (2.7)	4.0 (2.7)	4.7 (2.9)	0.04 [0.00;0.09]	.036	0.04 [0.00;0.09]	.045
Intercept						-1.40 [-1.81;-1.00]	<10 ⁻³

Abbreviations: aCoeff, adjusted probit coefficient; CI, confidence interval; Coeff, probit coefficient; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; ref., reference; SD, standard deviation; VAS, visual analog scale.

^aAdjusted for country of residence, seemingly unrelated bivariate probit, with the second equation for country of residence containing the explicative variables listed in the multivariable model in Table 1.

^bSeemingly unrelated bivariate probit, with the second equation for country of residence containing the explicative variables listed in the multivariable model in Table 1.

^cType of MS: relapsing–remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), unknown.

^dDisease disability score (adapted from the EDSS): no or minimal disability (0–2), moderate or substantial disability (3–7), total disability (8–10).

^eGlobal health level (VAS): from 0 (the worst imaginable health state) to 10 (the best imaginable health state).

^fMS-related pain level (VAS): from 0 (no pain) to 10 (extreme pain).

et al., 2021), lack of information on the practical use and efficacy of cannabis use for patients and doctors alike (Alexander, 2020; Temple et al., 2019), social or moral considerations (Page & Verhoef, 2006), and high prices.

We found that patients with MS in France use CBP for therapeutic purposes, and that cannabis herb/resin (mostly from street) and oil are the most common forms of CBP used. Herb/resin is also the most common form of CBP in Spain, far exceeding nabiximols, which can only be dispensed in the country's hospital pharmacies. While Canada, the USA and 23 European countries have approved several CBP, only five reviewed by Abuhasira et al. (2018) (Canada, Germany, Israel and the Netherlands, and over 50% of the states in the United States) have fully authorised the medical use of herbal cannabis. Moreover, those authors reported that most regulators allow physicians to decide what specific indications they will prescribe cannabis for (Abuhasira et al., 2018). This finding reflects a void in the counselling of physicians on cannabis use, as highlighted elsewhere (Calcaterra et al., 2020).

Our results add to the body of literature suggesting that cannabis and CBP use helps alleviate symptoms for patients with more severe MS. Physicians, if properly trained and brought up to date on CBP, can therefore be encouraged to explore MS patients' attitudes regarding cannabis and CBP use and, according to their disease severity and symptom patterns, can prescribe or counsel CBP and/or provide state-of-the-art information about the potential benefits of CBP use for therapeutic purposes. However, in the

context of France, none of this can happen before policy makers and law enforcers remove the legal barriers to cannabis and CBP use. Therefore, all healthcare professionals involved in MS patients care may participate in screening for and assessing cannabis use in those patients, keeping in mind that stronger pain and disability increase the likelihood of use. Moreover, as herb/resin is likely to be the most commonly used product, professionals' knowledge on harm reduction practices (Fischer et al., 2017; Meffert et al., 2019) may benefit to patients.

Setting up an appropriate regulation toward the therapeutic use of CBP would improve access to them, but would also avoid patients' exposure to uncontrolled and potentially adulterated and/or mislabeled CBP. This is for instance acutely needed in France, where cannabis flowers must come from the black market, which provides increasingly potent cannabis (Freeman et al., 2021).

We found that CBP use was lower in men than in women, which is inconsistent with results for cannabis from Canada (Clark et al., 2004), the UK (Ware et al., 2005) and the USA (Gupta et al., 2019). This difference may be related to the recent proliferation of CBD products (Walker et al., 2020), which can be legally sold in France and Spain, and which seem to attract more female than male buyers (Moltke & Hindocha, 2021; Wheeler et al., 2020).

To our knowledge, this is the first study to report the prevalence and correlates of CBP use in French patients with MS. Another strength is the international sampling design. By including patients from two countries—France and Spain—while statistically taking

TABLE 4 Factors associated with daily use of cannabis-based products in people with multiple sclerosis, accounting for differences in participants' characteristics by country of residence (seemingly unrelated bivariate probit regression, univariable and multivariable analyses, Carenity survey, $n = 641$).

	Daily use of cannabis-based products			Univariable analyses ^a	Multivariable analysis ^b		
	Total ($n = 641$)	No ($n = 541$)	Yes ($n = 100$)		p-value	aCoeff [95% CI]	p-value
	No. of participants (%) or mean (SD)	No. of participants (%) or mean (SD)	No. of participants (%) or mean (SD)				
Country of residence							
France (ref.)	447 (69.7)			1		1	
Spain	194 (30.3)			-0.27 [-0.98;0.43]	.445	0.32 [-0.53;1.17]	.461
Gender							
Female (ref.)	466 (72.7)	399 (73.7)	67 (67.0)	1			
Male	175 (27.3)	142 (26.2)	33 (33.0)	0.18 [-0.09;0.44]	.191		
Age (years)	47.1 (11.1)	47.1 (11.0)	47.5 (11.5)	-0.00 [-0.02;0.01]	.746		
Town/city size (no. of inhabitants)							
<1000 (ref.)	254 (39.6)	215 (39.7)	39 (39.0)	1			
10,000–100,000	226 (35.3)	193 (35.7)	33 (33.0)	0.06 [-0.24;0.35]	.712		
>100,000	161 (25.1)	133 (24.6)	28 (28.0)	0.26 [-0.10;0.63]	.154		
Educational level							
≤upper secondary school certificate (ref.)	330 (51.5)	283 (52.3)	47 (47.0)	1			
>upper secondary school certificate	311 (48.5)	258 (47.7)	53 (53.0)	0.13 [-0.10;0.37]	.275		
Time since diagnosis (years)	12.4 (9.2)	12.3 (9.1)	13.1 (9.6)	0.00 [-0.01;0.02]	.551		
Age at diagnosis (years)	34.7 (10.3)	34.8 (10.2)	34.4 (10.7)	-0.01 [-0.02;0.01]	.370		
MS-related spasticity							
Yes (ref.)	469 (73.2)	387 (71.5)	82 (82.0)	1			.033
No	98 (15.3)	91 (16.8)	7 (7.0)	-0.53 [-0.93;-0.13]	.009		
Unknown	74 (11.5)	63 (11.7)	11 (11.0)	-0.10 [-0.48;0.28]	.599		
Type of MS ^c							
RRMS (ref.)	365 (56.9)	315 (58.2)	50 (50.0)	1			
PPMS	95 (14.8)	78 (14.4)	17 (17.0)	0.24 [-0.14;0.61]	.223		
SPMS	135 (21.1)	105 (19.4)	30 (30.0)	0.39 [0.05;0.73]	.025		
Unknown	46 (7.2)	43 (8.0)	3 (3.0)	-0.39 [-0.98;0.19]	.190		
Disease disability score (adapted from the EDSS) ^d							
No or minimal disability (ref.)	184 (28.7)	166 (30.7)	18 (18.0)	1		1	.011

(Continues)

TABLE 4 (Continued)

	Total (n = 641) No. of participants (%) or mean (SD)	Daily use of cannabis-based products		Univariable analyses ^a Coeff [95% CI]	p-value	Multivariable analysis ^b	
		No (n = 541)	Yes (n = 100)			aCoeff [95% CI]	p-value
		No. of participants (%) or mean (SD)	No. of participants (%) or mean (SD)				
Moderate or substantial disability	349 (54.5)	291 (53.8)	58 (58.0)	0.40 [0.06;0.73]	.020	0.40 [0.06;0.73]	.020
Total disability	108 (16.8)	84 (15.5)	24 (24.0)	0.060 [0.20;0.99]	.003	0.60 [0.20;0.99]	.003
Global health level (VAS) ^c	5.9 (2.3)	5.9 (2.3)	5.7 (2.3)	-0.01 [-0.07;0.04]	.701		
MS-related level of pain (VAS) ^f	4.2 (2.7)	4.1 (2.7)	4.6 (3.0)	0.03 [-0.02;0.08]	.194		
Intercept						-1.43 [-1.84;-1.03]	<10 ⁻³

Abbreviations: aCoeff, adjusted probit coefficient; CI, confidence interval; Coeff, probit coefficient; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; ref., reference; SD, standard deviation; VAS, visual analogue scale.

^aAdjusted for country of residence, seemingly unrelated bivariate probit, with the second equation for country of residence containing the explicative variables listed in the multivariable model in Table 1.

^bSeemingly unrelated bivariate probit, with the second equation for country of residence containing the explicative variables listed in the multivariable model in Table 1.

^cType of MS: relapsing–remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), unknown.

^dDisease disability score (adapted from the EDSS): no or minimal disability (0–2), moderate or substantial disability (3–7), total disability (8–10).

^eGlobal health level (VAS): from 0 (the worst imaginable health state) to 10 (the best imaginable health state).

^fMS-related pain level (VAS): from 0 (no pain) to 10 (extreme pain).

into account the differences between socio-demographic and MS-related characteristics according to the country of residence, we highlighted correlates of CBP use common to both.

Our study sample cannot be considered representative of all Spanish or French patients with MS, and therefore we cannot generalise our results. More specifically, we recruited participants who were familiar with social media and internet platforms, and who engaged in community-based exchange. However, the fact that the majority of our study population were women with RRMS is consistent with the general features of populations with MS (Biernacki et al., 2020; Ramagopalan et al., 2010; Romanelli et al., 2020). Moreover, online surveying is likely to reduce the desirability bias which is expected to lead to under-reporting of CBP use, for instance in case of face-to-face interview with physician. Finally, MS-related disability was assessed through a self-administered questionnaire, and therefore, has not been clinically validated.

5 | CONCLUSION

To conclude, in a sample of French and Spanish patients with MS, patients experiencing higher levels of MS-related disability and/or pain were more likely to use CBP to alleviate their symptoms, and herb/resin was the most common form of administration. Further studies are needed to shed more light on patients' practices and on the clinical efficacy of cannabis-based treatments for MS-related symptoms. Results from these studies may encourage health authorities

to consider relaxing the barriers to cannabis use for MS patients in need for relief from pain.

6 | RELEVANCE TO CLINICAL PRACTICE

CBP are used by MS patients, especially those with more severe symptoms. There is a need to be aware of it and discuss this topic with them. Taking into account such use may help in properly assessing the patients' symptoms, as well as their unmet needs. Moreover, subsequent checking for drug–drug interactions between cannabinoids and current treatments may prevent drug-related risks. Finally, nurses and healthcare professionals may provide CBP and harm reduction counselling to optimise patients' benefits from such a use. When possible, access to safe CBP may be eased.

AUTHOR CONTRIBUTIONS

Project Conception: Tangui Barré, Damien Testa, Melina Santos, Fabienne Marcellin, Perrine Roux, Patrizia Carrieri, Lise Radoszycki and Camelia Protopopescu. *Project organisation:* Tangui Barré, Damien Testa, Melina Santos, Fabienne Marcellin, Perrine Roux, Patrizia Carrieri, Lise Radoszycki and Camelia Protopopescu. *Project execution:* Tangui Barré and Patrizia Carrieri. *Statistical analysis design:* Tangui Barré, Patrizia Carrieri and Camelia Protopopescu. *Statistical analysis–execution:* Camelia Protopopescu. *Statistical analysis–review and critique:* Tangui Barré and Camelia Protopopescu. *Preparation of the first draft of manuscript:* Tangui Barré. *Review and*

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest relevant to this work. The authors also declare that there are no additional disclosures to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki. According to French law and anonymity of data, no approval from ethics committee was needed. Informed written consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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