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ORIGINAL ARTICLE

Effects of THC/CBD oromucosal spray on spasticity-related symptoms in people with multiple sclerosis: results from a retrospective multicenter study

Francesco Patti[1] · Clara Grazia Chisari[1] · Claudio Solaro[2] · Maria Donata Benedetti[3] · Eliana Berra[4] · Assunta Bianco[5] · Roberto Bruno Bossio[6] · Fabio Buttari[7] · Letizia Castelli[8] · Paola Cavalla[9] · Raffaella Cerqua[10] · Gianfranco Costantino[11] · Claudio Gasperini[12] · Angelica Guareschi[13] · Domenico Ippolito[14] · Roberta Lanzillo[15] · Giorgia Teresa Maniscalco[16] · Manuela Matta[17] · Damiano Paolicelli[18] · Loredana Petrucci[19] · Simona Pontecorvo[20] · Isabella Righini[21] · Margherita Russo[22] · Francesco Saccà[15] · Giovanna Salamone[23] · Elisabetta Signoriello[24] · Gabriella Spinicci[25] · Daniele Spitaleri[26] · Eleonora Tavazzi[27] · Maria Trotta[28] · Mauro Zaffaroni[29] · Mario Zappia[1] · on behalf of the SA.FE. group

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Abstract

Introduction The approval of 9-δ-tetrahydocannabinol (THC)+cannabidiol (CBD) oromucosal spray (Sativex®) in Italy as an add-on medication for the management of moderate to severe spasticity in multiple sclerosis (MS) has provided a new opportunity for MS patients with drug-resistant spasticity. We aimed to investigate the improvement of MS spasticity-related symptoms in a large cohort of patients with moderate to severe spasticity in daily clinical practice.

Materials and methods MS patients with drug-resistant spasticity were recruited from 30 Italian MS centers. All patients were eligible for THC:CBD treatment according to the approved label: ≥ 18 years of age, at least moderate spasticity (MS spasticity numerical rating scale [NRS] score ≥ 4) and not responding to the common antispastic drugs. Patients were evaluated at baseline (T0) and after 4 weeks of treatment (T1) with the spasticity NRS scale and were also asked about meaningful improvements in 6 key spasticity-related symptoms.

Results Out of 1615 enrolled patients, 1432 reached the end of the first month trial period (T1). Of these, 1010 patients (70.5%) reached a ≥ 20% NRS score reduction compared with baseline (initial responders; IR). We found that 627 (43.8% of 1432) patients showed an improvement in at least one spasticity-related symptom (SRSr group), 543 (86.6%) of them belonging to the IR group and 84 (13.4%) to the spasticity NRS non-responders group.

Conclusion Our study confirmed that the therapeutic benefit of cannabinoids may extend beyond spasticity, improving spasticity-related symptoms even in non-NRS responder patients.

Keywords Multiple sclerosis · Clinical practice · Spasticity-related symptoms · THC · CBD

Introduction

Spasticity is a common and frequent disabling complication in multiple sclerosis (MS) patients and it is perceived as a continuous and/or sudden muscle rigidity [1, 2]. In a relevant proportion of MS patients, spasticity is responsible for worsening of other MS symptoms, interfering with a wide range of daily activities and increasing the burden of the disease not only for MS patients but also for caregivers [3, 4]. Indeed, several studies showed that the worsening of MS spasticity negatively impacts patients' quality of life [5, 6] and it is associated with a higher utilization of healthcare resources [6, 7].

Patti Francesco and G Chisari Clara contributed equally to this work.

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✉ Francesco Patti
patti@unict.it

Extended author information available on the last page of the article

Although there is a considerable heterogeneity in MS spasticity clinical expression [7, 8], in everyday practice, MS-related spasticity is closely associated either directly or indirectly to a wide array of other symptoms and functional impairments, such as cramps and nocturnal spasms, bladder disorders, pain, sleep disorders, and/or clonic movements, differing in presentation and severity [1]. A large cross-sectional survey-based study showed that the presence and severity of spasticity in a cohort of MS patients is significantly correlated to the worsening of the associated symptoms and of the functional impairment and, consequently, to a higher consumption of healthcare resources [6, 7].

The approval of 9-δ-tetrahydrocannabinol and cannabidiol (THC:CBD) oromucosal spray (Sativex®) in several European countries, as an add-on medication for the management of moderate to severe resistant generalized spasticity, has provided a new opportunity to treat MS patients reporting a spasticity not adequately responding to the first-line antispasticity drugs [9–13].

Several studies have demonstrated that THC and CBD are able to interact with human cannabinoid receptors 1 and 2 (CB_1 and CB_2), largely distributed in the central nervous system (CNS) pre-synaptic terminals, modulating the transmission of both excitatory and inhibitory pathways [10, 14, 15]. Accordingly, beyond spasticity, THC:CBD oromucosal spray has demonstrated clinically significant improvement in spasticity-related symptoms in several studies, demonstrating that its therapeutic effect may be involved either directly or by modulation of the nociceptive and the corticospinal pathways [16–19].

In Italy, the Agenzia Italiana del Farmaco (AIFA) states that MS patients eligible for starting THC:CBD as an add-on treatment must fulfill the following approved inclusion criteria: MS patients older than 18 years, with moderate to severe spasticity (0 ± 10 Numerical Rating Scale [NRS] score 4) and not responding to common and ongoing antispastic drugs (used under their approved label). After 4-week trial period, MS patients who do not reach a $\geq 20\%$ improvement (initial response, IR) in NRS were considered as "non-responders" and are no longer allowed to take THC:CBD (https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_003471_040548_RCP.pdf&retry=0&sys=m0b1l3).

Randomized clinical trials and observational studies have also confirmed that the 0–10 NRS, with the NRS percentage change (%Δ), is a reliable and valid patient-rated measure in assessing MS spasticity [20]. However, although MS patients seem to be able to selectively distinguish improvements in spasticity from other spasticity-related manifestations, such as pain [11], NRS does not take into account other symptoms occurring simultaneously and potentially influencing the perception of spasticity [20].

The aim of our study was to investigate the improvement of MS spasticity-related symptoms in a large cohort of patients with moderate to severe spasticity in daily clinical practice.

Materials and methods

Study population

This is the same population investigated in the multicenter observational study evaluating the effectiveness and tolerability of THC:CBD in a large prospective Italian MS population with drug-resistant spasticity, previously published [10, 21].

The study protocol was approved by the Policlinico-Vittorio Emanuele (Catania, Italy) Ethics Committee (number 37/2015/PO) and by the Ethics Committee of the other participating centers. All patients were informed about the study protocol and signed the informed consent. The data was collected from 1 January 2014 to the end of February 2015 in all the participating centers.

Patients recruited for the study were eligible for THC:CBD treatment according to the following approved label inclusion criteria established by AIFA and referred to the Summary of Product Characteristics: 18 years of age or older, moderate to severe spasticity (reported by the patients as a NRS score ≥ 4) not responding to the common antispastic drugs. We excluded patients with severe cardiovascular diseases, history of psychiatric diseases, previous and/or current use of street cannabis, and/or other psychoactive drugs and/or MS spasticity NRS score < 4 (https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_003471_040548_RCP.pdf&retry=0&sys=m0b1l3).

Patients eligible for the study were consecutively included in the Italian multicenter Sativex® dataset (SA.FE.) at the start of THC:CBD treatment (T0) and followed up after 4 weeks (T1) from baseline.

Data collection

We retrospectively analyzed the Italian multicenter dataset (SA.FE. group) collecting data about THC:CBD oromucosal spray effectiveness and tolerability in MS patients with drug-resistant spasticity from 30 Italian MS specialized centers [10, 21]. Demographical and clinical data, daily dose (number of puffs per day), clinical response to THC:CBD according to the AIFA criteria ($\geq 20\%$ NRS score reduction compared with baseline) were collected through patients' medical charts and AIFA registry. Subsequently, a data entry form was shared with the participating centers containing all the requested data.

In the current study, according to the THC:CBD effect on spasticity-related symptoms evolution, we divided our cohort in spasticity-related symptoms responders (SRSr) reporting an improvement in at least one spasticity-related symptom, and

spasticity-related symptoms non-responders (SRSnr) (Fig. 1). The effectiveness of THC:CBD in improving the spasticity-associated symptoms was assessed using an ad hoc interview, in which every patient was asked to indicate for each of the six pre-defined spasticity-related symptoms (spasms/cramps, clonic movements, sleep disturbances, urinary dysfunctions, pain, and depressed mood) the presence or absence of a meaningful amelioration. MS physical disability was evaluated using the Expanded Disability Status Scale (EDSS) by patients' center reports.

The validated 0–10 NRS patient-rated scale was used to assess MS spasticity and its evolution, at baseline (T0) and after 4 weeks (T1) from baseline [20]. NRS is an 11-point scale with scores ranging from 0 (no spasticity) to 10 (worst possible spasticity). Patients were asked to indicate on a scale of 0–10 the level of spasticity over the last 24 h. The raw score change in spasticity severity was calculated by subtracting the baseline from the follow-up value, while the percentage change was obtained by dividing the raw score change by the baseline value. In particular, for Sativex® effectiveness, the initial response threshold defined as ≥ 20% NRS spasticity score improvement versus the baseline value and a clinically relevant response threshold defined as ≥ 30% NRS spasticity score improvement versus baseline value, were evaluated [20].

Statistical analysis

In descriptive analyses, continuous variables were summarized as mean and standard deviation (SD) or median, and categorical variables were expressed as percentages. The numerical datasets were tested for normal distribution with the Shapiro-Wilk test. In case of abnormal distribution, appropriate non-parametric tests were performed. Nominal data was analyzed by Pearson's chi-square or Fisher's exact test where applicable. The correlation between NRS and clinical variables was carried out using a bivariate correlation (Pearson's or Spearman's correlation).

Unconditional logistic regression analyses were performed using binomial "spasticity-related symptoms responder yes/no" as dependent factor; we considered age, sex, disease duration, MS type, baseline EDSS, and baseline NRS as independent factors. All variables were included in the initial model and backward stepwise regression was performed. We included in the stepwise linear regression model all variables with $F \leq 1$ and $p \geq 0.01$, while variables with $F < 1$ and $p > 0.05$ were excluded. The selected variables were finally fitted in the stepwise multivariate regression models using multiple linear regression for continuous or ordinal outcomes and logistic regression for binary outcomes.

A p value equal to or lower than 0.05 was considered statistically significant.

The data was analyzed using the STATA V.12.0 software packages (StataCorp. 2011. Stata Statistical Software: Release 12. College Station TSL).

Results

The Italian multicenter dataset of THC:CBD included a total of 1615 patients with MS spasticity starting THC:CBD treatment and recruited from 30 large Italian MS centers (SA.FE group) distributed geographically across the nation. Data about effectiveness of THC:CBD, adverse events, percentage of patients discontinuing THC:CBD, and reasons of discontinuation have been previously reported [10, 21].

Based on the MS NRS spasticity, at T1, 1010 patients (70.5%) reached a ≥ 20% NRS score reduction (IRs) compared with baseline and were considered initial spasticity

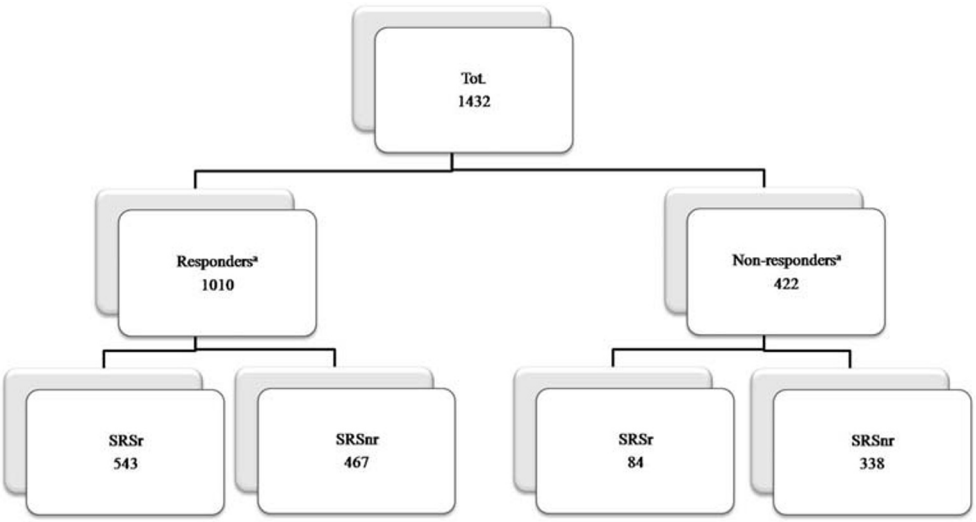

Fig. 1 Distribution of the cohort between responders[a] and non-responders[a] and between SRSr and SRSnr. [a]According to AIFA criteria of ≥ 20% reduction of NRS. SRSr, spasticity-related symptoms responders; SRSnr, spasticity-related symptoms not responders

responders according to the THC:CBD label and AIFA criteria (Fig. 1).

Among the 1432 patients (89.7% of 1615) reaching the end of the first month trial period (T1), we found that 627 (43.8%) patients showed an improvement in at least one spasticity-related symptom (SRSr group). Out of them, 543 (86.6%) of them belonging to the NRS spasticity initial responders group and 84 (13.4%) to the spasticity NRS non-responders group (Table 1, Fig. 1). No specific differences in terms of spasticity-related symptoms response were found among the participating centers.

The SRSr group showed statistically significant higher NRS mean score at T0 compared with SRSnr (8.2 vs. 7.6, Table 1; Fig. 2). Moreover, the SRSr group showed a statistically significant higher mean MS disease duration (18.1 vs. 16.8 years, $p < 0.05$) compared with the SRSnr group (Table 1).

In the whole population, 82 patients (13.1%) showed an improvement in only one MS spasticity-related symptom, 275 (43.8%) in two symptoms, 143 (22.8%) in three, and 127 (20.2%) in more than three symptoms investigated. Moreover, cramps/nocturnal spasms were reported as meaningfully ameliorated in 27.9% of patients, followed by bladder disorders (12.1%), and pain (11.5%) (Fig. 2).

According to the number of symptoms improved, the percentage of patients reporting more than three symptoms ameliorated was higher in the IRs group compared with the non-responders group (Fig. 3). Cramps/nocturnal spasms improved in 31.5% of the IRs, pain in 12.6%, and bladder disorders in 11.2%. Considering the 84 initial NRS non-responder patients, cramps/nocturnal spasms improved in 19.4%, pain in 14.2%, and bladder disorders in 9% (Table 2).

No correlations were found between spasticity-related symptoms improvement and other clinical and demographical data.

The multivariate analysis showed that progressive MS phenotype (OR 1.8, 95% CI 1.08 to 4.41, F value = 2.63, p = 0.03) and a higher NRS score at baseline (OR 1.4, 95% CI 1.2 to 5.11, F value = 2.41, $p = 0.05$) were both associated with an increased probability to report an amelioration in spasticity-related symptoms at T1.

Table 1 Clinical and demographical characteristics between SRSr and SRSnr groups

	SRSr	SRSnr	*P* value
N (%)	627 (43.8)	805 (56.2)	n.s.
Male (%)	298 (47.5)	375 (46.6)	n.s.
Female (%)	329 (52.5)	430 (53.4)	n.s.
Age (years, mean ± SD)	50.9 ± 9.7	50.9 ± 9.5	n.s.
Disease duration (years, mean ± SD)	18.1 ± 8.9	16.8 ± 8.5	< 0.05
Baseline EDSS (median, range)	6.4 ± 1.2	6.3 ± 1.1	n.s.
NRS score T0, baseline (mean ± SD)	8.2 ± 1.4	7.6 ± 1.3	< 0.05
NRS score T1, month 1 (mean ± SD)	5.4 ± 1.4	6.0 ± 1.8	n.s.
Dose, puffs number T1 (mean ± SD)	6.2 ± 2.4	6.9 ± 2.5	n.s.
MS phenotype			
RR	10 (1.6)	207 (25.7)	< 0.05
SP+PP	618 (98.4)	597 (74.2)	< 0.05
AIFA responders (%)	543 (86.6)	467 (58.0)	< 0.001

SRSr, spasticity-related symptoms responders; *SRSnr*, spasticity-related symptoms not responders; *MS*, multiple sclerosis; *EDSS*, expanding disability status scale; *NRS*, numerical rating scale; *RR*, relapsing remitting; *PP*, primary progressive; *RR*, relapsing remitting; *SP*, secondary progressive; *n.s.*, not significant

Discussion

Our study confirmed that the therapeutic benefit of THC:CBD oromucosal spray may extend beyond pure spasticity, ameliorating spasticity-related symptoms caused by MS. A relevant proportion (43.8%) of MS patients with moderate to severe treatment-resistant spasticity treated with this medication reported gaining meaningful symptomatic relief (SRS subgroup), improving in bladder control, sleep quality, pain, and/or mood. About 80% of these SRSr patients reported an amelioration in at least 2 spasticity-related symptoms.

In particular, our analyses focused on patients who reported an improvement in spasticity-related symptoms but not reaching the ≥ 20% NRS score reduction and, thus, considered to be non-responders according to the AIFA requirements. Indeed, we observed that even 19.9% of the patients considered non-responders to THC:CBD reported a meaningful improvement in one or more spasticity-related symptoms (Table 1, Fig. 1). It is to note that these patients are no longer allowed to continue THC:CBD treatment, according to the AIFA requirements.

Overall, it has been demonstrated that the effects of THC:CBD on spasticity-related symptoms could be explained by the direct interaction between cannabinoids and CB_1 and CB_2 receptors at pre-synaptic terminals in both the CNS and peripheral nociceptors that lead to the inhibition of the neuronal transmission in nociceptive pathways [19, 20]. Moreover, midbrain periaqueductal gray (PAG) and rostral ventromedial medulla, which modulate an efferent pathway projecting to brainstem and spinal cord nociceptive structures, express CB_1 and CB_2 receptors [19, 22–24]. In this sense, cannabinoids also seem to be able to inhibit the GABAergic input to this circuit facilitating the regulation of pain perception networks [25, 26].

In our cohort, cramps and spasms, clinically associated with a significant painful component, seemed to benefit from THC:CBD treatment in a large percentage of patients (27.9%), while clonic movements, less common but also causing spasticity-associated symptoms, improved in 4.5% of patients.

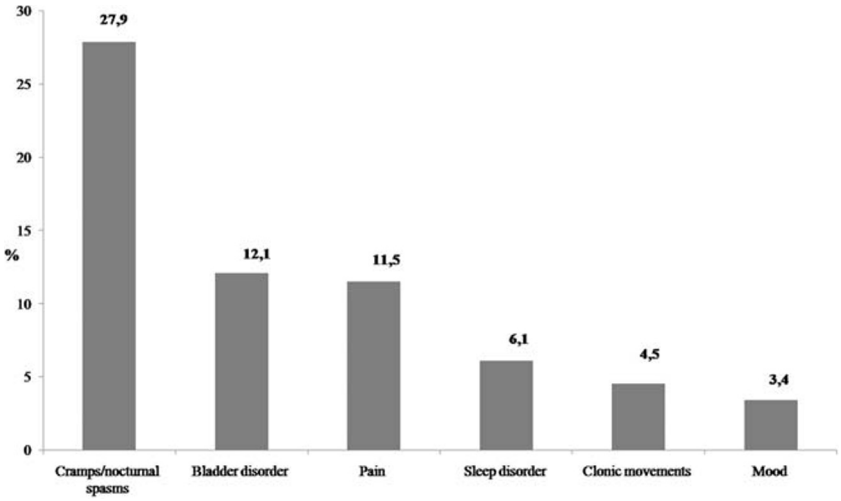

Fig. 2 Spasticity-related symptoms reported as improved in the study population

The cannabinoids and opioids anti-nociceptive properties of modulation in the PAG and rostral ventromedial medulla descending pathways, could explain the reduction of perceived pain in different patients (i.e., chronic neuropathic and non-cancer pain) treated with THC:CBD [9, 22, 25, 27]. In our study, pain improved meaningfully in 11.5% of included patients (Table 2).

Moreover, we found that 13.8% of our patients reported an ameliorated bladder function. A recent study has shown that THC:CBD directly improved overactive bladder symptoms in MS patients who did not respond to first-line therapies [28, 29]. It is conceivable that THC:CBD may directly act on CB_1 receptors expressed on bladder and uterus. Indeed, both relaxation and contraction effects on bladder strips could be mediated by THC at transient receptor potential vanilloid 1 (TRPV1) receptors, with the result of a release of calcitonin gene-related peptide [30]. Finally, cannabidiol seems to have an anti-hyperalgesic action that is also mediated by TRPV1 receptors [31].

Our results showed that about 6% of our patients reported an amelioration in sleep quality. The efficacy of THC:CBD on sleep-related quality in MS has already been assessed in a 14-week treatment study, but data were only presented for the NRS IRs [32]. The same mechanisms described above could also explain the effect on sleep disturbances since the reduced pain perception, less rigidity, and lower spasms count could contribute in improving the quality of sleep [33].

A novel result coming from our analysis is that NRS alone does not seem to be enough as the only instrument to assess response to THC:CBD. Aligned to our observation, a recent study showed the positive impact of the THC:CBD oromucosal spray on patients' ambulation abilities both in the NRS responder and non-responder patients [34]. These latter results cast further doubts on the

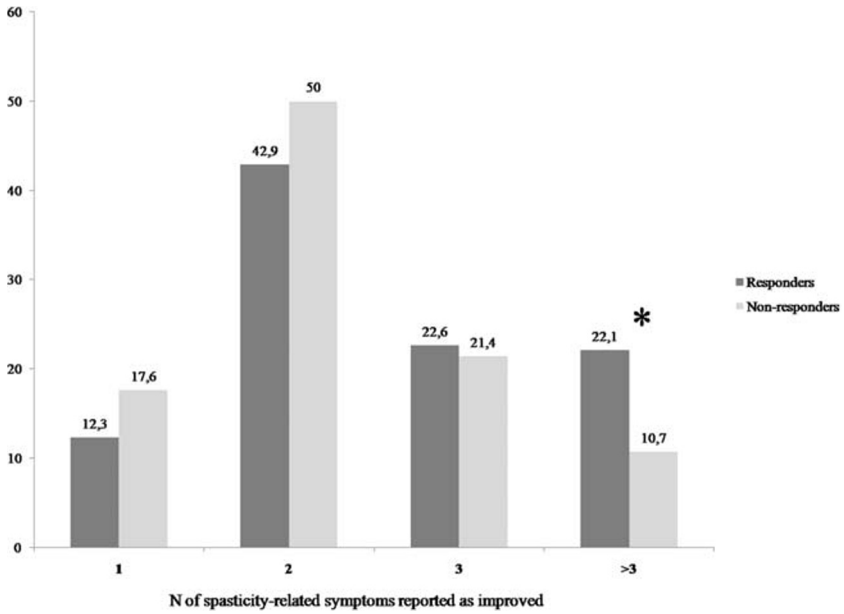

Fig. 3 Number of the symptoms reported as improved between SRSr and SRSnr. SRSr, spasticity-related symptoms responders; SRSnr, spasticity-related symptoms not responders. *$p < 0.05$

Table 2 Patterns of spasticity-related symptoms reported as improved in responders and non-responders patients

Symptoms	Spasticity responders[a] (1010, 70.53%)	Spasticity non-responders[a] (422, 29.47%)	*P* value
1 or more symptoms improved, N (%)	544 (53.9)	84 (19.9)	< 0.05
Cramps/nocturnal spasms (%)	318 (31.5)	82 (19.4)	< 0.01
Bladder disorder (%)	113 (11.2)	60 (14.2)	n.s.
Pain (%)	127 (12.6)	38 (9.0)	n.s.
Sleep disorder (%)	51 (5.0)	36 (8.5)	n.s.
Clonic movements (%)	53 (5.2)	11 (2.6)	n.s.
Mood (%)	42 (4.2)	11 (2.6)	n.s.

[a] According to criteria of ≥ 20% reduction of MS spasticity NRS score vs. baseline

n.s., not significant

use of NRS as a single scale for the comprehensive evaluation of the response to the THC:CBD treatment. In line with a recent review [22], we found that the percentage of patients reporting an improvement in spasticity-related symptoms was higher in the IRs group than in the NRS non-responder group (Table 2).

Furthermore, no statistical differences were found in the percentage of patients reporting at least one, two, and three symptoms improved between the NRS IRs and non-responder groups (Fig. 2), leading us to consider that the improvement of MS spasticity-associated symptoms with cannabinoids is not only due to the effects of THC:CBD on spasticity. This last finding emphasizes the need of new and more comprehensive multifactorial tools evaluating THC:CBD treatment response, that take into account the wide variability of MS spasticity, its associated symptoms, and even their impact on patients' quality of life and health perception.

Since direct correlations between MS spasticity severity and worsening of spasticity-associated symptoms and consumption of health-related resources have been demonstrated [7], it is conceivable that a treatment producing clinically meaningful symptomatic improvement across multiple domains could also increase patients' autonomy, enhancing the performance in activities of daily living and, in consequence, improving their quality of life.

Although this is a large study reporting THC:CBD experience in daily clinical practice, our results may be affected by the observational nature of our study. In particular, the non-randomized design of the study, the lack of a control group and of information of the baseline prevalence of each MS spasticity-associated symptoms, has prevented the evaluation of the evolution of these manifestations. Secondly, the improvement of spasticity-related symptoms was assessed verbally during the T1 follow-up visits and without the application of specific questionnaires and/or scales. However, in order to attempt to mitigate this bias, a data entry form was shared with the participating centers containing the requested data.

As the retrospective nature of the study, the effectiveness of THC:CBD in improving the spasticity-associated symptoms was assessed during the clinical interview, after the 4-week trial period. Every patient was asked to indicate the presence or absence of a meaningful amelioration in one or more of predefined spasticity-related symptom. Thus, as the lack of data about the prevalence of the spasticity-related symptoms at baseline, our results are not able to draw conclusions about the effect of THC:CBD treatment on spasticity-related symptoms. Future prospective studies using validated ad hoc questionnaire are needed in order to address these issues. Moreover, whether the benefits of THC:CBD on associated symptoms/functional measures demonstrated in our study were a direct effect or secondary to the relief of general spasticity cannot be ruled out on the basis of our data. Indeed, it is also conceivable that a global measure, such as the NRS, should be able to detect perceived improvements in other domains not included in the six pre-defined questions used in our study. However, the finding that non-responder patients may have benefits in improving spasticity-related symptoms highlights the inability of NRS to catch all the facets of MS spasticity. Another limitation was the lack of comparing NRS values with other objective measures of spasticity (such as Ashworth scale, stretch reflexes evaluation, neurophysiological measures, corticospinal excitability measurement, etc). Although, in the current literature, these attempts have shown conflicting results [13, 35, 36]. Finally, the follow-up period duration of 4 weeks could be insufficient to assess long-term effects of THC:CBD on spasticity-related symptoms and further research is needed to address this issue.

In conclusion, our study suggested that the combination drug therapy may enhance efficacy by targeting multiple mechanisms involved not only in spasticity, but also in its associated symptoms [25]. We demonstrated that 19.9% patients, not reaching the ≥ 20% NRS score reduction and, thus, considered non-responders, reported an amelioration in at least one of spasticity-related symptoms. So, we raised the questions: is the NRS evaluation alone enough to distinguish

between who is a "responder" from who is not? Is it correct to consider and use, in clinical practice, just one patient reported outcome? May it be more advisable to include in a clinical practice spastic-related symptoms ad hoc questionnaire administered by clinicians and complementing the NRS evaluation? As known, patients and doctors do not agree on clinical outcomes [37].

Based on our findings, the improvement of spasticity-related symptoms in non-responder patients may suggest that it would be worth maintaining THC:CBD therapy for a period longer than 4 weeks.

In the future, randomized-controlled studies, comparing objective assessment to NRS, should be performed to investigate the eventual efficacy of THC:CBD on spasticity-related symptoms in NRS non-responder patients.

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Contributorship statement Prof. Patti F contributed to the study plan, realized database, interpreted data, drafted the manuscript, discussed results with the authors involved in the protocol, approved the final manuscript, and took the responsibility for the submission.

Dr. Chisari CG contributed to the study plan, collected and handled database, performed statistical analysis, drafted and approved the manuscript.

Dr. Solaro C contributed to the study design, collected data at his site, interpreted data, and approved the manuscript.

Drs. Benedetti MD, Berra E, Bianco A, Bruno Bossio R, Buttari F, Castelli L, Cavalla P, Cerqua R, Costantino GF, Gasperini C, Guareschi A, Ippolito D, Lanzillo R, Maniscalco GT, Matta M, Messina S, Paolicelli D, Petrucci L, Pontecorvo S, Righini I, Russo M, Saccà F, Salamone G, Signoriello E, Spinicci G, Spitaleri D, Tavazzi E, Trotta M, Zaffaroni M collected data at their respective sites, shared data results and interpretation of the results, and approved the final manuscript.

Prof. Zappia M interpreted and discussed with the Corresponding Author the results obtained, and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Prof Patti has received honoraria for speaking activities by Bayer Schering, Biogen Idec, Merck Serono, Novartis, and Sanofi Aventis; he also served as advisory board member the following companies: Bayer Schering, Biogen Idec, Merck Serono, and Novartis; he was also funded by Pfeizer and FISM for epidemiological studies; finally, he received grant for congress participation from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Aventis, and TEVA. Dr. Chisari CG received grant for congress participation from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Aventis, and TEVA. Dr. Solaro received honoraria from Biogen, Genzyme, Novartis, Merck Serono, Almirall, Roche, and TEVA. Dr. Bruno Bossio R received grant for advisory board activities from Almirall. Dr. Maniscalco GT received speaking and advisory honoraria from Biogen, Novartis, and TEVA. Dr. Matta M received honoraria for serving in the scientific advisory boards of Almirall, Novartis, Biogen, and Genzyme. Prof. Zappia M has received compensation for consulting services from Boehringer-Ingelheim, Lundbeck, Union Chimique Belge, and scientific grants from AIFA - Agenzia Italiana del Farmaco, Novartis, Lundbeck.

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Ethics approval The study was approved by the Policlinico-Vittorio Emanuele (Catania, Italy) Ethics Committee (no. 37/2015/PO) and by the Ethics Committee of the other participating centers.

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Affiliations

Francesco Patti[1] · Clara Grazia Chisari[1] · Claudio Solaro[2] · Maria Donata Benedetti[3] · Eliana Berra[4] · Assunta Bianco[5] · Roberto Bruno Bossio[6] · Fabio Buttari[7] · Letizia Castelli[8] · Paola Cavalla[9] · Raffaella Cerqua[10] · Gianfranco Costantino[11] · Claudio Gasperini[12] · Angelica Guareschi[13] · Domenico Ippolito[14] · Roberta Lanzillo[15] · Giorgia Teresa Maniscalco[16] · Manuela Matta[17] · Damiano Paolicelli[18] · Loredana Petrucci[19] · Simona Pontecorvo[20] · Isabella Righini[21] · Margherita Russo[22] · Francesco Saccà[15] · Giovanna Salamone[23] · Elisabetta Signoriello[24] · Gabriella Spinicci[25] · Daniele Spitaleri[26] · Eleonora Tavazzi[27] · Maria Trotta[28] · Mauro Zaffaroni[29] · Mario Zappia[1] · on behalf of the SA.FE. group

1 Department "G.F. Ingrassia", section of Neurosciences, University of Catania, Catania, Italy

2 Department of Neurology, ASL3 Genovese, and Department of Rehabilitation, ML Novarese Hospital Moncrivello, Genoa, Italy

3 Department of Neuroscience, Biomedicine, and Movement Sciences, Section of Neurology, University of Verona, Verona, Italy

4 Neurorehabilitation Unit, Department of Neurology, Neurology Institute C. Mondino, Pavia, Italy

5 Multiple Sclerosis Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

6 Neurology Operating Unit and Multiple Sclerosis Center, Provincial Health Authority of Cosenza, Cosenza, Italy

7 Synaptic Immunopathology Lab, Department of Systems Medicine, Tor Vergata University, Rome, Italy

8 Neurology Unit, IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

9 Department Neuroscience and Mental Health, Multiple Sclerosis Centre, Health and Science City University Hospital of Turin, Turin, Italy

10 Department of Experimental and Clinical Medicine, Neurological Clinic, Marche Polytechnic University, Ancona, Italy

11 Demyelinating Diseases Centre, Foggia Hospital, Foggia, Italy

12 Multiple Sclerosis Centre, San Camillo-Forlanini Hospital, Rome, Italy

13 Multiple Sclerosis Center, Medicine Department, Fidenza Hospital, Fidenza, PR, Italy

14 Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

15 Department of Neurosciences, Reproductive and Odontostomatological Sciences, University Federico II, Naples, Italy

16 Department of Neurology, Ospedale Cardarelli, Naples, Italy

17 Neurobiology Unit, Neurologia 2, CReSM (Regional Referring Center Multiple Sclerosis), San Luigi Gonzaga University Hospital & Neuroscience Institute Cavalieri Ottolenghi (NICO), Orbassano, TO, Italy

18 Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, Bari, Italy

19 Multiple Sclerosis Centre, University Hospital Pisa, Pisa, Italy

20 Multiple Sclerosis Center of Department of Neurology and Psychiatry of Sapienza, University of Rome, Rome, Italy

21 Department of NEUROFARBA, University of Florence, Florence, Italy

22 Multiple Sclerosis Centre, IRCCS-Bonino Pulejo Centre, Messina, Italy

23 Neuroimmunology Unit, Villa Sofia-Cervello Hospital, Palermo, Italy

24 Department of Clinical and Experimental Medicine, Multiple Sclerosis Center, II Division of Neurology, University of Campania "Luigi Vanvitelli", Naples, Italy

25 Department of Medical Sciences and Public Health, Multiple Sclerosis Center, University of Cagliari, Cagliari, Italy

26 Azienda Ospedaliera di Rilievo Nazionale, San Giuseppe Moscati, Avellino, Italy

27 Multiple Sclerosis Center, Unit of Motor Neurorehabilitation, IRCCS Santa Maria Nascente, Fondazione Don Gnocchi, Milan, Italy

28 Institute of Neurology, University "Magna Graecia", Germaneto, Catanzaro, Italy

29 Multiple Sclerosis Center, ASST della Valle Olona, Gallarate Hospital, Gallarate, VA, Italy