frontiers in Neurology

HYPOTHESIS AND THEORY
published: 17 March 2020
doi: 10.3389/fneur.2020.00152

The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms

Óscar Fernández[1], Lucienne Costa-Frossard[2], Marisa Martínez-Ginés[3], Paloma Montero[4], José Maria Prieto[5] and Lluis Ramió[6]*

[1] Biomedical Research Institute of Malaga, University of Málaga, Málaga, Spain, [2] Department of Neurology, Ramón y Cajal University Hospital, Madrid, Spain, [3] Department of Neurology, Gregorio Marañón Hospital, Madrid, Spain, [4] Servicio de Neurología, Hospital Clínico San Carlos, Madrid, Spain, [5] Servicio de Neurologia, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain, [6] Servicio de Neurologia, Hospital Universitari de Girona Doctor Josep Trueta, Girona, Spain

OPEN ACCESS

Edited by:
Letizia Leocani, San Raffaele Hospital (IRCCS), Italy

Reviewed by:
Angel Perez Sempere, Hospital General Universitario de Alicante, Spain
Bruno Gran, Nottingham University Hospitals NHS Trust, United Kingdom

***Correspondence:**
Óscar Fernández
oscar.fernandez.sspa@gmail.com

Specialty section:
This article was submitted to Multiple Sclerosis and Neuroimmunology, a section of the journal Frontiers in Neurology

Received: *22 August 2019*
Accepted: *14 February 2020*
Published: *17 March 2020*

Citation:
Fernández Ó, Costa-Frossard L, Martínez-Ginés M, Montero P, Prieto JM and Ramió L (2020) The Broad Concept of "Spasticity-Plus Syndrome" in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms. Front. Neurol. 11:152. doi: 10.3389/fneur.2020.00152

Multiple sclerosis (MS) pathology progressively affects multiple central nervous system (CNS) areas. Due to this fact, MS produces a wide array of symptoms. Symptomatic therapy of one MS symptom can cause or worsen other unwanted symptoms (anticholinergics used for bladder dysfunction produce impairment of cognition, many MS drugs produce erectile dysfunction, etc.). Appropriate symptomatic therapy is an unmet need. Several important functions/symptoms (muscle tone, sleep, bladder, pain) are mediated, in great part, in the brainstem. Cannabinoid receptors are distributed throughout the CNS irregularly: There is an accumulation of CB_1 and CB_2 receptors in the brainstem. Nabiximols (a combination of THC and CBD oromucosal spray) interact with both CB_1 and CB_2 receptors. In several clinical trials with Nabiximols for MS spasticity, the investigators report improvement not only in spasticity itself, but also in several functions/symptoms mentioned before (spasms, cramps, pain, gait, sleep, bladder function, fatigue, and possibly tremor). We can conceptualize and, therefore, hypothesize, through this indirect information, that it could be considered the existence of a broad "Spasticity-Plus Syndrome" that involves, a cluster of symptoms apart from spasticity itself, the rest of the mentioned functions/symptoms, probably because they are interlinked after the increase of muscle tone and mediated, at least in part, in the same or close areas of the brainstem. If this holds true, there exists the possibility to treat several spasticity-related symptoms induced by MS pathology with a single therapy, which would permit to avoid the unnecessary adverse effects produced by polytherapy. This would result in an important advance in the symptomatic management of MS.

Keywords: multiple sclerosis, spasticity, symptomatic therapy, symptom cluster, symptomatic treatment

In the last two decades, the availability of new disease-modifying therapies has radically changed the management of multiple sclerosis (MS) and relapsing–remitting MS in particular (1), resulting in a longer life expectancy for patients with the disease (2). Nevertheless, MS currently remains incurable and, in most patients, disability will eventually progress and they must live with the very many symptoms associated with the disease. These symptoms can have a major impact on patient's quality of life (3) and their management is considered important, although traditionally, this area has received far less attention than disease-modifying therapies (4).

A wide range of treatments are available to manage each of the MS symptoms (5–7). Given that different agents are used for different symptoms and a patient may have several symptoms present at the same time, many MS patients are multi-medicated, particularly as most patients will also be receiving disease-modifying therapies. This article will assess the current fragmented approaches to pharmacological management of spasticity muscle tone increase-related symptoms and their shortcomings. Given that the treatment of MS-associated muscle spasticity has been associated in a good number of clinical trials and also observational studies with the improvement of several other functions/symptoms present in MS (8), we will conceptualize, and subsequently hypothesize, about the clinical interest of introducing the more broad concept of "Spasticity-Plus Syndrome" to provide a unified framework for managing all these seemingly related functions/symptoms. By applying such a concept, it would be possible to simplify the management of symptoms associated with MS and reduce importantly the interactions and adverse effects associated with poly-medication.

MS SYMPTOMS

MS pathology affects multiple areas of the central nervous system (CNS), producing therefore a multiplicity of symptoms that can be basically classified as sensory alterations, fatigue, importantly cognitive dysfunction, pain (both paroxysmal and persistent), visual and brainstem symptoms (diplopia, oscillopsia, facial sensory symptoms, vertigo, and dizziness, nausea and vomiting, instability, etc.), those relating to mobility (spasticity, weakness, ataxia and tremor, impaired ambulation, and hand function), psychologic/psychiatric alterations (anxiety, depression, etc.), bowel, sexual and bladder dysfunctions, sleep disorders, and paroxysmal symptoms (seizures, dysarthria, etc.). All these symptoms vary along the course of the disease, being more prevalent as the disease evolves (**Table 1**) (9–12) (**Figure 1**).

Spasticity, a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes, due to the interruption of craniocaudal pathways by MS lesions at different CNS levels, is a very frequent symptom in patients with this disease. A large survey in the United States found 84% of patients with MS with some form of spasticity, with severity ranging from minimal (31%) to total (4%) (12). Similar results were obtained in a recent survey in the United Kingdom, which reported some form of spasticity in 86% of patients with MS (13). Another survey from the United Kingdom found that 47% of randomly selected patients with MS had clinically significant spasticity, defined as modified Ashworth scale score of 2, 3, or 4 (14). Spasticity is an important symptom of MS because it has a negative effect on mobility and can be painful (15, 16), which in turn is ranked highly as a concern among patients with MS and is considered to have a large impact on quality of life (3, 17, 18). Moreover, the muscle rigidity and spasms of spasticity trigger, worsen, or are associated to other functions/symptoms in MS subjects beyond mobility impairment, such as fatigue (3), sleep disorders, and bladder dysfunction (19) (**Figure 2**).

Ataxia, reported in up to 80% of MS patients at some point in their disease (20), and tremor, detected in more than a half of subjects in a sample of randomly selected patients with MS in a British study (21), are also impairing symptoms that can impact mobility.

Bladder symptoms have been reported in approximately three-quarters of patients with MS (22), while sexual dysfunction was found to be present in 84% of men and 85% of women (23). Both types of dysfunction can have a marked impact on quality of life, including among patients with otherwise low disability (24). Bowel dysfunction (including both constipation and fecal incontinence) was reported in 68% of an unselected patient population with MS (25).

Fatigue, depression, and cognitive impairment are also highly prevalent among patients with MS and impact quality of life even after accounting for physical disability (26, 27). Central pain in MS can be as severe as that associated with arthritic conditions (28) and the need for treatment may be underestimated.

In summary, symptoms of MS are widespread, varied, often interlinked, and highly prevalent among patients with the disease. The impact on quality of life is substantial, and mobility is a concern for patients (16, 17). MS symptoms have been cited as

TABLE 1 | The percentage of symptoms present in multiple sclerosis vary along the course of the disease [adapted from (9–12)].

Symptom	% (At onset-advanced)
Sensory alterations	85–94
Fatigue	79–96
Cognitive dysfunction	63–81
Pain	57–85
Visual and brainstem symptoms (scotoma, diplopia, oscillopsia, vertigo, dizziness, etc.)	55–92
Motor alterations: spasticity, ataxia, tremor, impaired ambulation	50–91
Psychologic/psychiatric alterations (anxiety, depression, etc.)	50–79
Bowel alterations	41–82
Sexual dysfunction	40–90
Urinary dysfunction	40–87
Sleep disorders	40–60
Paroxysmal symptoms (seizures, dysarthria, etc.)	30–81

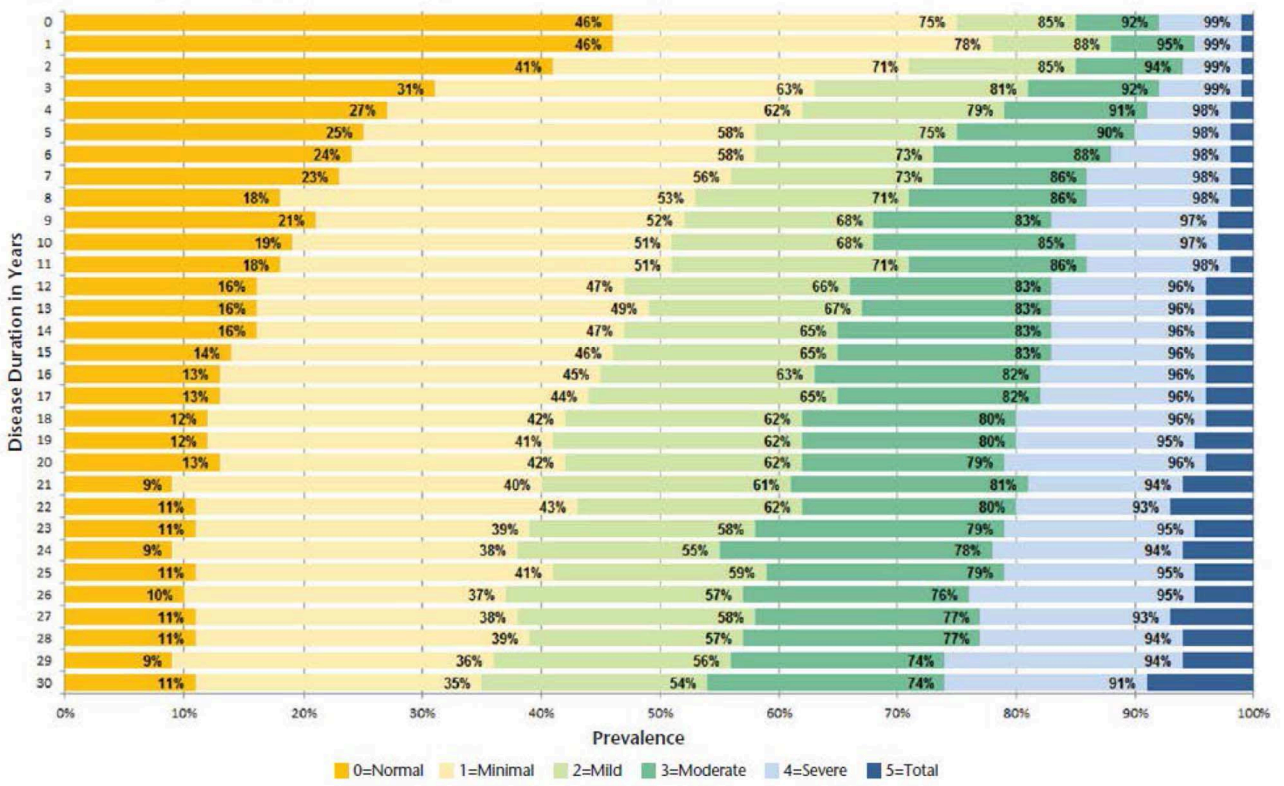

FIGURE 1 | Spasticity prevalence according to disease duration in years ($N = 23,842$). With permission (9).

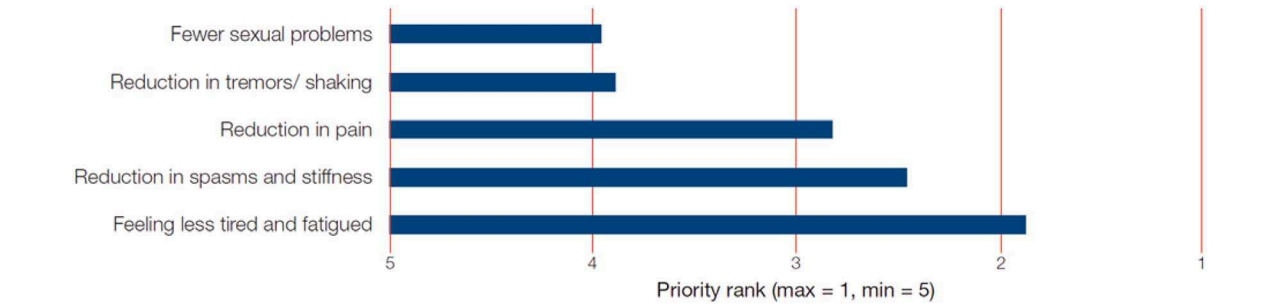

FIGURE 2 | Symptom reduction priorities for patients. With permission (18).

a major barrier for employment (29). Appropriate management of these symptoms is therefore imperative.

MANAGEMENT OF SPASTICITY SYMPTOMS

As detailed above, the symptoms of MS are varied and substantially impact patients' well-being. Management of symptoms is, however, a complex task requiring a multidisciplinary approach. In some cases, non-pharmacological interventions may be beneficial, e.g., physiotherapy for spasticity, but might have a limited time effect and the evidence supporting such approaches is not always strong (30), and pharmacological interventions are often considered necessary. As shown in **Table 2**, a wide variety of agents can be used (31, 32).

Any pharmacological intervention has a risk of side effects (**Table 3**) and this risk is accentuated by drug–drug interaction possibilities. In some cases, the side effects from a drug to treat one MS symptom may exacerbate another symptom produced by the disease. For example, a number of treatments used for spasticity, fatigue, pain, and depression can all cause erectile dysfunction and decreased libido (**Table 4**) (33). An approach

TABLE 2 | Commonly used pharmacological treatments for MS symptoms [adapted from (31, 32)].

Symptom	Pharmacological treatment
MOBILITY-RELATED SYMPTOMS	
Spasticity	Baclofen, tizanidine, nabiximols (THC:CBD), benzodiazepines (diazepam, clonazepam), gabapentin, dantrolene, botulinum toxin A (local treatment), intrathecal baclofen
Ataxia and tremor	Propranolol, clonazepam, levetiracetam, isoniazid, carbamazepine, ondansetron, dolasetron, cannabinoids, glutethimide
Impaired ambulation	Aminopyridines (fampridine)
BLADDER, BOWEL, AND SEXUAL DYSFUNCTION	
Urinary dysfunction	*Bladder inefficiency:* α1-blockers (indoramin) *Bladder overactivity:* antimuscarinics, intravesical botulinum toxin A, desmopressin, cannabinoids, intravesical vanilloids
Bowel dysfunction	Bulking agents, Laxatives
Sexual dysfunction	Sildenafil, tadalafil, vardenafil
FATIGUE, COGNITIVE IMPAIRMENT, AND MOOD DISTURBANCE	
Fatigue	Amantadine, modafinil, pemoline, aminopyridine, carnitine
Cognitive dysfunction	Acetylcholinesterase inhibitors, memantine, amantadine, pemoline, gingko biloba, L-amphetamine sulfate
Mood disturbance	Fluoxetine, sertraline, moclobemide
PAIN	
Paroxysmal pain	Carbamazepine, oxcarbazepine, lamotrigine, gabapentin, topiramate, misoprostol
Persistent pain	Amitriptyline, pregabalin, gabapentin, lamotrigine, levetiracetam, cannabinoids
VISUAL AND BRAINSTEM SYMPTOMS	
Visual dysfunction	Memantine, gabapentin
Brainstem-related symptoms	Antiepileptic drugs
SLEEP DISORDERS	
Excessive sleepiness	Modafinil
Restless legs syndrome	Dopaminergic agonists

that would simplify the management of the diverse symptoms of MS-associated spasticity could potentially be beneficial for the patient.

THE BROAD CONCEPT OF "SPASTICITY-PLUS SYNDROME" IN MS

A syndrome in medicine is classically defined as a combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disease or disorder (34). Usually, these signs and/or symptoms would be considered to have a common underlying pathophysiology, or respond to a given therapy, although the clinical manifestations could be varied. In MS, spasticity is thought ultimately to arise from damage to motor areas or pathways, at multiple possible levels, in the CNS, leading to dynamic changes in motor circuit function

TABLE 3 | Main side effects of commonly used treatments for spasticity according to the EU Summary of Product Characteristics.

Baclofen	**Side effects:** depression, fatigue, ataxia, and tremor **Warnings:** Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment **Drug–drug interactions:** muscle relaxants (such as tizanidine), with synthetic opiates or with alcohol, tricyclic antidepressants, anti-hypertensives
Tizanidine	**Side effects**: somnolence, dizziness, fatigue **Drug-drug interactions:** CYP inhibitors, antihypertensives, oral contraceptives
Nabiximols (THC:CBD)	**Side effects:** application site reactions, dizziness, fatigue, anxiety, disorientation, rare possibility of falls **Drug–drug interactions:** CYP inhibitor (ketoconazole, fluconazole, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort), alcohol, contraceptives
Diazepam	**Side effects:** Confusion, drowsiness, ataxia, impaired motor ability, tremor, fatigue, withdrawal symptoms **Drug–drug interactions:** alcohol, neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, baclofen tizanidine
Clonazepam	**Side effects:** Impaired concentration, restlessness, confusional state and disorientation, somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia, light-headedness, co-ordination disturbances, fatigue and muscle weakness **Drug–drug interactions:** wide range of potential interactions with different classes of drug
Gabapentin	**Side effects:** confusion and emotional lability, depression, anxiety, nervousness, somnolence, dizziness, ataxia, convulsions, hyperkinesia, dysarthria, amnesia, tremor, insomnia, headache, coordination abnormal, nystagmus, increased, decreased, or absent reflexes, visual disturbances, diplopia, vertigo, arthralgia, myalgia, back pain, twitching, impotence, fatigue **Drug–drug interactions:** Opioids
Carbamazepine	**Side effects:** Ataxia, dizziness, somnolence; diplopia, headache; fatigue **Drug–drug interactions:** inhibitors or inducers of CYP 3A4
Levetiracetam	**Side effects:** Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, somnolence, headache, convulsion, balance disorder, dizziness, lethargy, tremor, asthenia/fatigue **Drug–drug interactions:** anti-epileptic medications
Dantrolene	**Side effects:** depression, confusion, insomnia, nervousness; seizure, visual disturbances, speech disturbances, headache **Drug–drug interactions:** non-depolarizing muscle relaxants
Botulinum toxin A	**Side effects:** Somnolence, gait disturbance, paresthesia (dependent on site of administration) **Drug–drug interactions:** Potentially with agents with neuromuscular blocking effects

TABLE 4 | Adverse sexual function effects of drugs used in the symptomatic treatment of MS [adapted from (33)].

Symptoms of MS	Treatment	Adverse sexual function effects associated with treatment
Cognitive dysfunction	Donepezil	N/A
Spasticity	Baclofen	ED, inability to ejaculate (rare)
	Tizanidine	Urinary frequency, urgency, incontinence, urinary retention
	Dantrolene	
	Clonidine	
	Benzodiazepines	Decreased libido, ED, retrograde ejaculation
		N/A
		N/A
Fatigue	Amantadine	Decreased libido
	Modafinil	N/A
	Methylphenidate	N/A
	Amphetamine/ dextroamphetamine	ED, changes in libido (dose dependent)
Pain	Tricyclic antidepressants	ED, ejaculatory impairment, anorgasmia, decreased libido
	Valproic acid	ED
	Carbamazepine	ED
	Oxcarbazepine	N/A
	Lamotrigine	ED
	Gabapentin	N/A
	Duloxetine	Decreased libido, ED, ejaculation dysfunction and anorgasmia
Bladder and bowel dysfunction	Anticholinergic medication	Dry mouth, vaginal dryness, constipation
Depression	SSRIs	Decreased libido, anorgasmia, delayed ejaculation
	Bupropion	N/A
	Venlafaxine	ED, anorgasmia

ED, erectile dysfunction; MS, multiple sclerosis; N/A, not applicable; SSRIs, selective serotonin reuptake inhibitors.

and muscle tone that affect neuronal circuits and thereby cause spasticity (35). Bladder dysfunction in MS is originally caused by damaged neural pathways between the pons and sacral spinal cord, in turn impairing bladder function (36). Likewise, progressive demyelination and axonal or neuronal damage of the CNS leads to fatigue (37) and cognitive impairment (28). The presence of spasticity has been associated with worsening of other functions/symptoms in an epidemiological study of spasticity in MS (spasms, pain, bladder dysfunction, and sleep alterations) (3, 19) (**Figure 3**).

Although the specific mechanisms of the above symptoms might vary, damage to the CNS is common to all of them and we could consider, for practical reasons, as forming part of a syndrome, in which we would denote this new broad "Spasticity-Plus Syndrome" as a useful concept to be used in the symptomatic management in MS. This could be considered as an extension of the definition of symptom clusters or complexes, which underscores two primary features that have been defined as the existence of "three or more symptoms (e.g., pain, fatigue, sleep insufficiency) that are related to each other and that the symptoms must be inter-related through a common etiology or statistically as a cluster or latent variable. Such concurrent symptoms likely have a synergistic influence on behavioral, functional, and QOL outcomes and co-occurring symptoms seemingly provide a more efficient target for management than a single, isolated symptom taken out of its clinical context" (38).

The framing of MS symptoms within a syndrome also implies that a single intervention, in this case one that targets the cannabinoid system, a widely distributed molecular system in the CNS, may potentially influence a range of different symptoms. The presence in MS patients of one or more of the symptoms contained in the broad "Spasticity-Plus Syndrome" concept (spasticity and/or spasms-cramps and/or pain and/or bladder dysfunction and/or sleep disorders and/or fatigue and/or tremor) would have to trigger in physicians the search of the other symptoms' presence and severity and the attempt to manage them as appropriately as possible with proven, well-tolerated, and as simple as possible to use options.

The cannabinoid system is present in the brain, spinal cord, and peripheral nerves and comprises the cannabinoid receptors, CB_1 and CB_2, along with their ligands, the endocannabinoids, which are derived from fatty acids (39, 40). CB_1 receptors are widely distributed within the CNS on nerve terminals, including areas associated with movement, postural control, pain and sensory perception, memory, cognition, emotion, appetite, and autonomic and endocrine function. A particularly high accumulation of CB_1 and CB_2 receptors is found in the brainstem where important functions/symptoms such as spasticity, sleep, bladder, and pain are mediated (41). CB_2 receptors are mainly involved in regulating cytokine release from immune cells and immune cell migration in a manner that appears to reduce inflammation and certain kinds of pain (42). In short, the possible new and broad concept of "Spasticity-Plus Syndrome" in MS may point us toward an approach for simplifying management of MS symptoms (**Figure 4**).

CANNABINOIDS FOR THE TREATMENT OF FUNCTIONS/SYMPTOMS BELONGING TO THE BROAD "SPASTICITY-PLUS SYNDROME"

Several randomized clinical trials have demonstrated improvement in resistant spasticity symptoms, in patients with MS following add-on treatment with an oromucosal spray containing a 1:1 mixture of 9-δ-tetrahydocannabinol and cannabidiol (THC:CBD) (43–47).

This benefit for spasticity has also been reported in very many observational trials in the clinical practice setting (48). Studies of THC:CBD for the treatment of MS symptoms, other than spasticity itself, are fewer and often beset with design limitations, such as small number of patients. Nevertheless, large THC:CBD studies that collected evolution of pain, sleep disorders, and bladder dysfunction as secondary endpoints do point to a potential benefit for these symptoms (43–46). A substudy of the ***CA****nnabinoids for treatment of spasticity and other symptoms related to* ***M****ultiple* ***S****clerosis* study ("CAMS") (49)

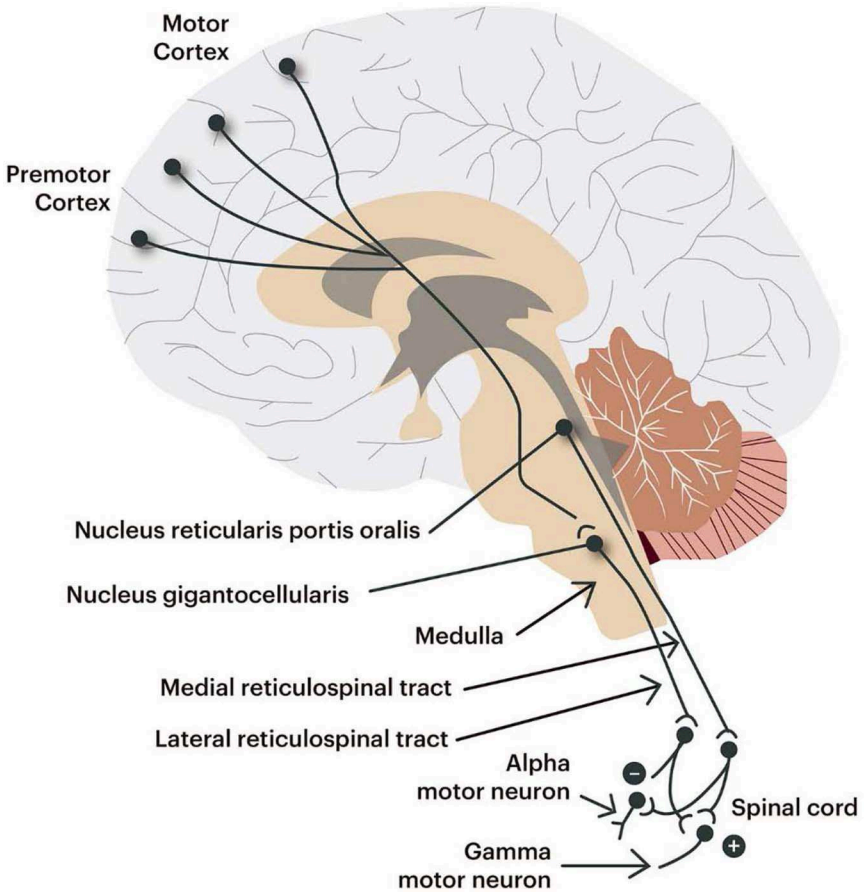

FIGURE 3 | Areas of the CNS mediating spasticity.

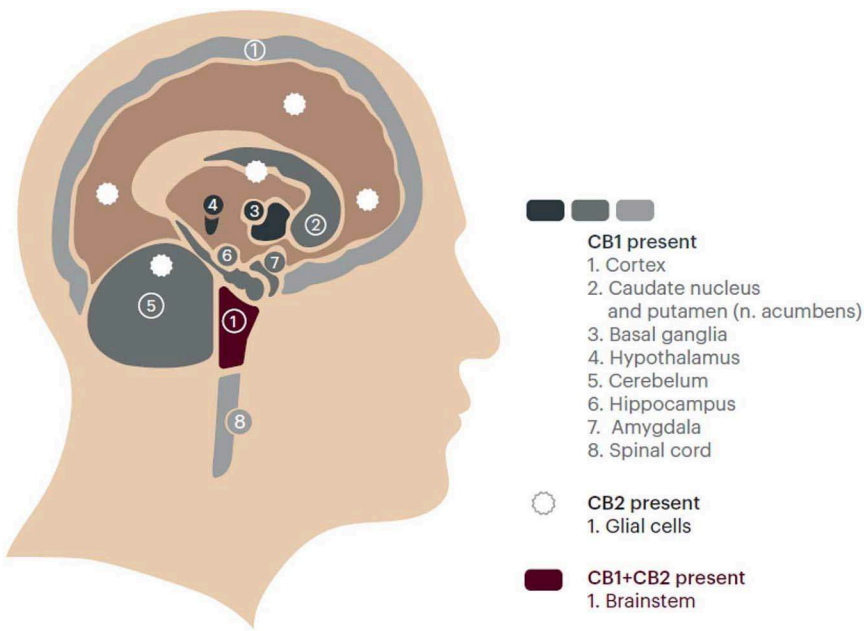

FIGURE 4 | Distribution of cannabinoid receptors (CB1 and CB2) in the central nervous system (The Endocannabinoid System). Redrawn from https://www.fundacion-canna.es/en/endocannabinoid-system. Accessed April 06, 2019). With permission.

found significant benefit in the control of incontinence, although THC-only tolerability profile is less interesting than the THC and CBD combination (50, 51). In the case of MS-associated pain, a systematic review of randomized clinical trials of cannabinoid treatments concluded that these agents are effective in alleviating pain (52). There is thus evidence that THC:CBD can be used to treat a variety of MS spasticity-associated and somehow related symptoms (53). Moreover, application of the possible new broad concept of "Spasticity-Plus Syndrome" in MS would suggest an appropriate line of investigation, in patients with more than one symptom that could be amenable to a single therapy, to simplify symptom management.

As a clear limitation, we consider this as a preliminary conceptual proposal that has to be sustained in the future with new studies, not yet available, and that could give more background and support to our concept, so that the hypothesis would be testable and be a promising area of research in the field of symptomatic therapy. Another limitation is the fact that we do not know whether this concept could be applied to the spasticity present in other diseases such as spinal cord injury, stroke, etc., as it has not been surveyed yet as far as we know.

CONCLUSIONS

The numerous and varied symptoms associated with MS requires complex management with multiple drugs, all with potential side effects that may exacerbate other symptoms and with potential drug–drug interactions. Recognition that a good number of MS symptoms might have a common or close underlying pathophysiology, or respond to a single therapy, in the form of a new broad "Spastic-Plus Syndrome" in MS may help simplify treatment of these symptoms with agents such as cannabinoids that target CB_1 and CB_2 receptors.

AUTHOR CONTRIBUTIONS

ÓF, LC-F, MM-G, PM, JP, and LR contributed conception and design of the study. ÓF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

Almirall S.A. provided funding and logistical support for the project but did not participate in the conception, writing, or decisions taken.

ACKNOWLEDGMENTS

We acknowledge Greg Morley, MD (Docuservicio), for technical assistance in the writing of this article.

REFERENCES

1. Ransohoff RM, Hafler DA, Lucchinetti CF. Multiple sclerosis-a quiet revolution. *Nat Rev Neurol.* (2015) 11:134–42. doi: 10.1038/nrneurol.2015.14
2. Lunde HMB, Assmus J, Myhr K-M, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatr.* (2017) 88:621–5. doi: 10.1136/jnnp-2016-315238
3. Flachenecker P, Henze T, Zettl UK. Spasticity in patients with multiple sclerosis–clinical characteristics, treatment and quality of life. *Acta Neurol Scand.* (2014) 129:154–62. doi: 10.1111/ane.12202
4. Fox RJ, Thompson A, Baker D, Baneke P, Brown D, Browne P, et al. Setting a research agenda for progressive multiple sclerosis: the international collaborative on progressive MS. *Mult Scler.* (2012) 18:1534–40. doi: 10.1177/1352458512458169
5. Ben-Zacharia AB. Therapeutics for multiple sclerosis symptoms. *Mt Sinai J Med.* (2011) 78:176–91. doi: 10.1002/msj.20245
6. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. *Lancet Neurol.* (2010) 9:1182–99. doi: 10.1016/S1474-4422(10)70249-0
7. Toosy A, Ciccarelli O, Thompson A. Symptomatic treatment and management of multiple sclerosis. In: Goodin DS, editor. *Handbook of Clinical Neurology Multiple Sclerosis Related Disorders,* 3rd series, Vol. 122. Amsterdam: Elsevier B.V (2014). p. 514–61.
8. Marková J. Newest evidence for tetrahydrocannabinol:cannabidiol oromucosal spray from randomized clinical trials. *Neurodegener Dis Manag.* (2019) 9:9–13. doi: 10.2217/nmt-2018-0050
9. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. *Int J MS Care.* (2013) 15:146–56. doi: 10.7224/1537-2073.2012-053
10. Sastre-Garriga J, Tintoré M, Nos C, Tur C, Río J, Téllez N, et al. Clinical features of CIS of the brainstem/cerebellum of the kind seen in MS. *J Neurol.* (2010) 257:742–6. doi: 10.1007/s00415-009-5403-0
11. Nociti V, Losavio FA, Gnoni V, Losurdo A, Testani E, Vollono C, et al. Sleep and fatigue in multiple sclerosis: a questionnaire-based, cross-sectional, cohort study. *J Neurol Sci.* (2017) 372:387–92. doi: 10.1016/j.jns.2016.10.040
12. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult Scler Houndmills Basingstoke Engl.* (2004) 10:589–95. doi: 10.1191/1352458504ms1085oa
13. Milinis K, Tennant A, Young CA, TONiC study group. spasticity in multiple sclerosis: associations with impairments and overall quality of life. *Mult Scler Relat Disord.* (2016). 5:34–9. doi: 10.1016/j.msard.2015.10.007
14. Barnes MP, Kent RM, Semlyen JK, McMullen KM. Spasticity in multiple sclerosis. *Neurorehabil Neural Repair.* (2003) 17:66–70. doi: 10.1177/0888439002250449
15. Sosnoff JJ, Gappmaier E, Frame A, Motl RW. Influence of spasticity on mobility and balance in persons with multiple sclerosis. *J Neurol Phys Ther JNPT.* (2011) 35:129–32. doi: 10.1097/NPT.0b013e31822a8c40
16. Zwibel HL. Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. *Adv Ther.* (2009) 26:1043–57. doi: 10.1007/s12325-009-0082-x
17. Heesen C, Böhm J, Reich C, Kasper J, Goebel M, Gold SM. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler Houndmills Basingstoke Engl.* (2008) 14:988–91. doi: 10.1177/1352458508088916
18. Heller M, Taylor D. *Greater Expectations: The Future Hopes of People With Multiple Sclerosis.* (2017). Available online at: https://pdfs.semanticscholar.org/866a/959d88a224883f7e9dd5ddbec31017f36bac.pdf
19. Oreja-Guevara C, González-Segura D, Vila C. Spasticity in multiple sclerosis: results of a patient survey. *Int J Neurosci.* (2013) 123:400–8. doi: 10.3109/00207454.2012.762364
20. Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. *Cochrane Database Syst Rev.* (2007) 24:CD005029. doi: 10.1002/14651858.CD005029.pub2
21. Alusi SH, Worthington J, Glickman S, Bain PG. A study of tremor in multiple sclerosis. *Brain J Neurol.* (2001) 124:720–30. doi: 10.1093/brain/124.4.720
22. DasGupta R, Fowler CJ. Bladder, bowel and sexual dysfunction in multiple sclerosis: management strategies. *Drugs.* (2003) 63:153–66. doi: 10.2165/00003495-200363020-00003

23. Tepavcevic DK, Kostic J, Basuroski ID, Stojsavljevic N, Pekmezovic T, Drulovic J. The impact of sexual dysfunction on the quality of life measured by MSQoL-54 in patients with multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl.* (2008) 14:1131–6. doi: 10.1177/1352458508093619
24. Nortvedt MW, Riise T, Myhr KM, Landtblom AM, Bakke A, Nyland HI. Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. *Mult Scler Houndmills Basingstoke Engl.* (2001) 7:231–5. doi: 10.1177/135245850100700404
25. Hinds JP, Eidelman BH, Wald A. Prevalence of bowel dysfunction in multiple sclerosis. a population survey. *Gastroenterology.* (1990) 98:1538–42. doi: 10.1016/0016-5085(90)91087-M
26. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler.* (2003) 9:219–27. doi: 10.1191/1352458503ms904oa
27. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* (2008) 7:1139–51. doi: 10.1016/S1474-4422(08)70259-X
28. Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. *Mult Scler.* (2005) 11:322–7. doi: 10.1191/1352458505ms1168oa
29. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol.* (2010) 257:926–36. doi: 10.1007/s00415-009-5441-7
30. Amatya B, Khan F, Galea M. Rehabilitation for people with multiple sclerosis: an overview of cochrane reviews. *Cochr Database of Syst Rev*. (2019) 1:CD012732. doi: 10.1002/14651858.CD012732.pub2
31. Newsome SD, Aliotta PJ, Bainbridge J, Bennett SE, Cutter G, Fenton K, et al. A framework of care in multiple sclerosis, part 2: symptomatic care and beyond. *Int J MS Care.* (2017) 19:42–56. doi: 10.7224/1537-2073.2016-062
32. Oreja-Guevara C, Montalban X, de Andrés C, Casanova-Estruch B, Muñoz-García D, García I, et al. Consensus document on spasticity in patients with multiple sclerosis. grupo de enfermedades desmielinizantes de la sociedad española de neurología. *Rev Neurol.* (2013) 57:359–73. doi: 10.33588/rn.5708.2013374
33. Fletcher SG, Castro-Borrero W, Remington G, Treadaway K, Lemack GE, Frohman EM. Sexual dysfunction in patients with multiple sclerosis: a multidisciplinary approach to evaluation and management. *Nat Clin Pract Urol*. (2009) 6:96–107. doi: 10.1038/ncpuro1298
34. The British Medical Association. *Illustrated Medical Dictionary*. London: Dorling Kindersley (2002). p. 177–536.
35. Patejdl R, Zettl UK. Spasticity in multiple sclerosis: contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions. *Autoimmun Rev.* (2017) 16:925–36. doi: 10.1016/j.autrev.2017.07.004
36. Betts CD, D'Mellow MT, Fowler CJ. Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatr.* (1993) 56:245–50. doi: 10.1136/jnnp.56.3.245
37. Patejdl R, Penner IK, Noack TK, Zettl UK. Multiple sclerosis and fatigue: a review on the contribution of inflammation and immune-mediated neurodegeneration. *Autoimmun Rev.* (2016) 15:210–20. doi: 10.1016/j.autrev.2015.11.005
38. Motl RW, Suh Y, Weikert M. Symptom cluster and quality of life in multiple sclerosis. *J Pain Symptom Manage*. (2010) 39:1025–32. doi: 10.1016/j.jpainsymman.2009.11.312
39. Svízenská I, Dubový P, Sulcová A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures–a short review. *Pharmacol Biochem Behav.* (2008) 90:501–11. doi: 10.1016/j.pbb.2008.05.010
40. Howlett AC. The cannabinoid receptors. *Prostaglandins Other Lipid Mediat.* (2002) 68–69:619–31. doi: 10.1016/S0090-6980(02)00060-6
41. van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science.* (2005) 310:329–32. doi: 10.1126/science.1115740
42. Baker D, Jackson SJ, Pryce G. Cannabinoid control of neuroinflammation related to multiple sclerosis. *Br J Pharmacol.* (2007) 152:649–54. doi: 10.1038/sj.bjp.0707458
43. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms inmultiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler.* (2004) 10:434–41. doi: 10.1191/1352458504ms1082oa
44. Collin C, Davies P, Mutiboko IK, Ratcliffe S. Sativex spasticity in MS study group. randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol.* (2007) 14:290–6. doi: 10.1111/j.1468-1331.2006.01639.x
45. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al. A double-blind, randomized, placebo-controlled, parallel-group study of sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res.* (2010) 32:451–9. doi: 10.1179/016164109X12590518685660
46. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol*. (2011) 18:1122–31. doi: 10.1111/j.1468-1331.2010.03328.x
47. Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci.* (2019) 129:119–28. doi: 10.1080/00207454.2018.1481066
48. Fernández O. Advances in the management of MS spasticity: recent observational studies. *Eur Neurol.* (2014) 72(Suppl. 1):12–4. doi: 10.1159/000367618
49. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. (2003) 362:1517–26. doi: 10.1016/S0140-6736(03)14738-1
50. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct.* (2006) 17:636–41. doi: 10.1007/s00192-006-0086-x
51. Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler.* (2010) 16:1349–59. doi: 10.1177/1352458510378020
52. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin.* (2007) 23:17–24. doi: 10.1185/030079906X158066
53. Arroyo R, Vila C, Dechant KL. Impact of Sativex(®) on quality of life and activities of daily living in patients with multiple sclerosis spasticity. *J Comp Eff Res.* (2014) 3:435–44. doi: 10.2217/cer.14.30

Conflict of Interest: ÓF has received honoraria as consultant in advisory boards, as chair/lecturer in meetings, from participation in clinical trials and other research projects promoted by Actelion, Allergan, Almirall, Bayer-Schering, Biogen, Merck Serono, Novartis, Sanofi Genzyme, Roche, Teva, Orizon, and Araclon, and research support from the Hospital Foundation FIMABIS. LC-F has received compensation for consulting services and speaking fees from Merck, Novartis, Biogen, Bayer, Sanofi, Genzyme, TEVA, Almirall, Biopas, Ipsen, Celgene, and Mylan. MM-G has received compensation for consulting services and speaking fees from Merck, Biogen, Novartis, Sanofi-Genzyme, Almirall, Roche, and Teva. PM has received compensation for consulting services and speaking fees from Almirall. JP has done consultancy work for Bayer HealthCare, Biogen, Genzyme, Novartis, Sanofi-Aventis, Teva, Roche, Merck, and Almirall; has given lectures in congresses and symposia organized by Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva Pharmaceuticals; and has received funding for research projects from Almirall, Biogen, Novartis, and Sanofi-Genzyme. LR has received compensation for consulting services and speaking fees from Biogen, Novartis, Bayer, Merck, Sanofi, Genzyme, TEVA, Almirall, and Mylan.