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To cite this article: Michelle H. Cameron, Francois Bethoux, Edelle Field-Fote, William R. Lenderking, Erica Zaiser, Katelyn N. Cutts, Joanne M. Wagner, Joris Berwaerts & Joshua R. Steinerman (22 Jul 2023): Development of an integrated conceptual model of multiple sclerosis spasticity, *Disability and Rehabilitation*, DOI: [10.1080/09638288.2023.2237403](https://doi.org/10.1080/09638288.2023.2237403)

To link to this article: <https://doi.org/10.1080/09638288.2023.2237403>



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RESEARCH ARTICLE



Development of an integrated conceptual model of multiple sclerosis spasticity

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ABSTRACT

Purpose: Spasticity is common in multiple sclerosis (MS), often leading to functional limitations and disability. We developed a conceptual model of spasticity in MS integrating expert opinion, recent literature, and experiences of clinicians and people with MS spasticity.

Methods: A conceptual model was developed based on a targeted literature review of articles published between 2014 and 2019, followed by input from clinicians, then input from participants with MS spasticity. Multidisciplinary experts on spasticity provided guidance at each step.

Results: Key concepts of the integrated spasticity conceptual model included: moderators; triggers; modifiers; treatment; objective manifestations; subjective experience; physical, functional, social, and emotional/psychological impacts; and long-term consequences. Participants with MS spasticity most frequently endorsed spasms, tightness, and pain as descriptors of spasticity. Some participants with MS spasticity had difficulty distinguishing spasticity from other MS symptoms (e.g. muscle weakness). Some triggers, emotional/psychological impacts, and long-term consequences of spasticity reported by participants with MS spasticity were not previously identified in the published literature.

Conclusions: This conceptual model of spasticity, integrating published literature with the experience of clinicians, people with MS spasticity, and experts, demonstrates the complex, multidimensional nature of MS spasticity. This model may be used to improve clinician-patient dialogue, research, and patient care.

> IMPLICATIONS FOR REHABILITATION

- Many people with multiple sclerosis (MS) have spasticity, generally in the lower limbs, but this symptom is complex and multidimensional and therefore difficult to characterize.
- MS spasticity may be influenced by moderators, triggers, modifiers, and treatment, all of which can affect objective measures and the subjective experience of spasticity.
- MS spasticity can have physical, functional, social, and emotional/psychological impacts as well as long-term consequences that can affect rehabilitation and ultimately reduce health-related quality of life for people with MS.
- Given that people with MS may view spasticity differently than their rehabilitation providers, providers should ask patients about their spasticity, including their moderators, triggers, modifiers, experience, impacts, long-term consequences, and effects on quality of life.
- This conceptual model provides a framework to improve clinician-patient dialogue, research, and rehabilitation for MS spasticity.

ARTICLE HISTORY

Received 3 February 2022

Revised 13 June 2023

Accepted 13 July 2023

KEYWORDS

Multiple sclerosis; muscle spasticity; conceptual model; qualitative research; interviews


Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system resulting in a variety of symptoms and often leading to functional impairment [1, 2]. In 2017, it was estimated that there were over 900,000 people with MS (PwMS) in the United States [3]. Up to 80% of PwMS experience spasticity, a complex and multidimensional symptom [4]. Spasticity is challenging to characterize. Physiologic and environmental variables can trigger spasticity, and PwMS may experience spasticity in various ways [5, 6]. Published studies that highlight the perspectives of PwMS on spasticity and its impact

on health-related quality of life are limited [7]. Since input from both PwMS and clinicians is needed to ultimately improve dialogue between PwMS and their healthcare providers, research is needed to better understand how PwMS and clinicians view MS spasticity based on their respective experiences.

The purpose of this study was to develop a conceptual model of MS spasticity that integrates perspectives from recent peer-reviewed literature with those of clinicians, people with MS spasticity, and multidisciplinary experts in the field of spasticity from academia and industry. This integrated conceptual model provides a framework for describing and understanding spasticity in PwMS.

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 Supplemental data for this article can be accessed online at <https://doi.org/10.1080/09638288.2023.2237403>.

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Methods

Overview of study design

This study used qualitative methods to develop a conceptual model of MS spasticity using a multistep iterative process (Figure 1). Relevant peer-reviewed literature was reviewed to produce an initial conceptual model. Clinician feedback was then used to revise this initial conceptual model and to develop a guide for interviews of PwMS with spasticity. Semi-structured interviews with PwMS and spasticity were conducted to further refine and finalize the conceptual model. At each step, input was provided by the six authors who are experts on spasticity from different disciplines, including neurology, psychiatry, and physical therapy (JB, JRS, JMW, FB, MC, and EFF; Figure 1).

Targeted literature review

A targeted literature search of PubMed of English language papers on MS spasticity was performed. Only randomized controlled trials, other interventional studies, observational studies, and review articles were included. Abstracts were included if they were published within the five years prior to when the project was initiated (January 1, 2014 through September 3, 2019). The complete search strategy for this targeted literature review is available in Supplemental Table 1. This resulted in 282 abstracts. Two authors reviewed these abstracts independently for inclusion in the full-text literature review. Abstracts were excluded if they described animal studies, did not mention symptoms or impacts of spasticity, or did not mention spasticity. Of the 282 abstracts retrieved, 29 met these criteria and were reviewed as full-text articles. Of the 29 reviewed articles, only 19 described spasticity in terms of symptoms, impacts, and other concepts of interest and provided insights across MS and other key indications. The spasticity experts were asked to identify additional key references, including seminal papers published outside the screening publication time window and papers referred to by the identified publications. This yielded an additional four articles for a total of 23 articles. Additionally, a desk review of patient organization websites (National Multiple

Sclerosis Society [www.nationalmssociety.org]) and the Multiple Sclerosis Trust [www.mstrust.org.uk]) was conducted to identify any additional patient-friendly spasticity descriptors and impacts. These were used to develop the initial conceptual model of MS spasticity.

Interviews with MS clinicians

Three clinicians who treat PwMS at different institutions were individually interviewed via telephone using a semi-structured interview guide. Their identities were not disclosed to the sponsor. Each interview lasted approximately one hour. The interviews focused on the key characteristics of spasticity and how, in their experience, PwMS describe symptoms of spasticity. These clinicians also gave feedback on the relevance and completeness of the initial conceptual model based on the literature review. The interviews were audio recorded. These clinician interviews and subsequent discussions with the experts in spasticity were the basis for initial refinements to the conceptual model which was used to develop a semi-structured patient interview guide.

Interviews with people with spasticity due to MS

Twenty patients with clinician-diagnosed MS of any subtype with MS-related spasticity were individually interviewed via telephone using a patient interview guide. Their identities were not disclosed to the sponsor. The interview took approximately 90 min. The interviews focused on the patients' experience of spasticity and its impacts. The interviews were audio recorded and transcribed.

Study enrollment

Potential participants with clinician-diagnosed MS-related spasticity were referred by their clinician to a third-party recruitment vendor independent of the study sponsor. The referring clinician confirmed the diagnosis of MS and spasticity and provided additional clinical details. Alternatively, participants could share further details on their diagnosis via screenshots of medical records,

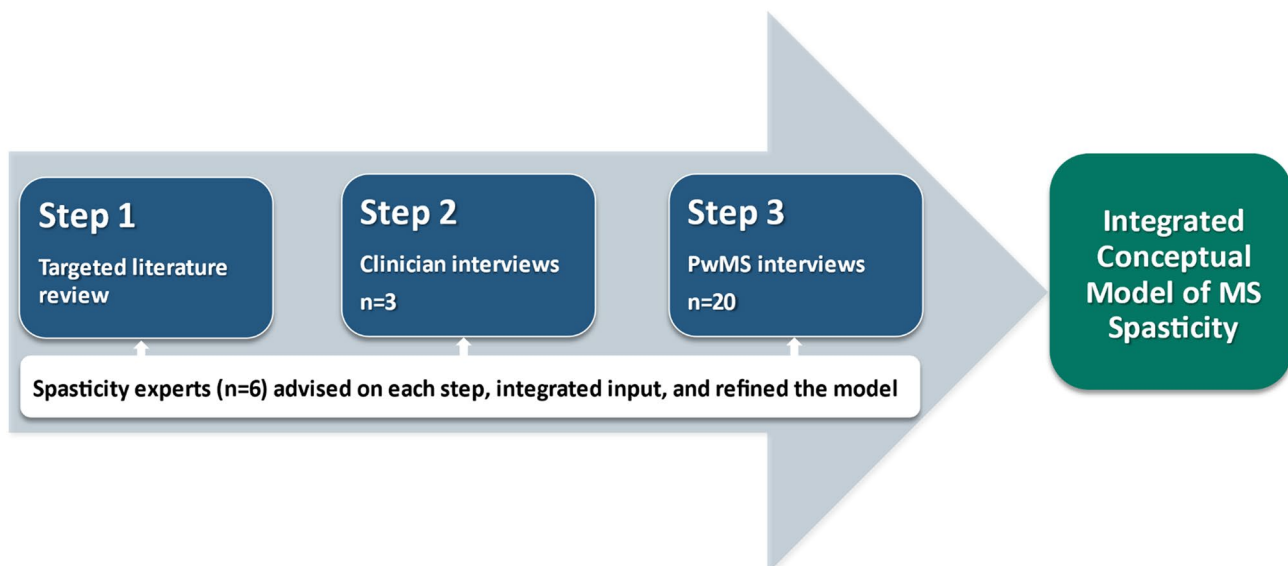


Figure 1. Steps in developing the integrated conceptual model of multiple sclerosis spasticity. PwMS=people with multiple sclerosis.

confirmation letter from the clinician, or other confirmatory documentation. Potential participants were screened for eligibility prior to the interview. Participants were eligible if they were ≥ 18 years old, could read and write English, were diagnosed with MS of any subtype for ≥ 12 months, and had spasticity due to MS for ≥ 6 months prior to the study as determined by the referring clinician. Exclusion criteria included any comorbid disorder of the central nervous system, a diagnosis of clinically isolated syndrome, or an impairment (e.g. visual) that could interfere with study participation.

Potential participants were recruited during regularly scheduled patient clinical visits (in person or via telehealth) or by phone. Interested PwMS were invited to contact the recruitment vendor to schedule an interview. Written consent was provided by participants at the time of the interview; participants confirmed consent verbally to be audio recorded. Participants were remunerated for their time. This study received ethics approval from an independent institutional review board (Advarra Pro00045192).

Interviews

The interviews were conducted by four trained research staff with experience in qualitative methods. The semi-structured interview guide was used to draw out the participants' experience of spasticity. Participants were first asked how long they had been diagnosed with MS, what symptoms they typically experienced in relation to spasticity, where those symptoms occurred in their body, and what spasticity meant to them. Additional questions focused on understanding the triggers of spasticity, how long the symptoms lasted, and how daily functioning was affected. Participants were also asked to comment on whether spasticity caused or worsened other symptoms, such as pain, fatigue, or sexual dysfunction. Participants were then asked to describe their spasticity experience and were probed using the key concepts identified in the literature or during the clinician interviews as necessary for further elucidation or clarification. Interviews were continued until saturation was reached. Saturation was defined as the point at which no substantially new themes, descriptions of a concept, or terms were introduced as additional interviews were conducted [8].

After the interviews, participants were asked to complete the following forms and assessments: a sociodemographic and clinical information form, the Patient Determined Disease Steps (PDDS) [9], and Spasticity Numeric Rating Scale (NRS-S). The NRS-S was a single question asking, "On a scale of 0 to 10, please indicate your level of spasticity over the last 24h, considering 0 as 'no spasticity' and 10 as 'worst possible spasticity'".

Data analysis

The patient participant interview transcripts were reviewed and the content coded for concepts by trained coders. The codes were then entered into a saturation grid to track and tally identified concepts. Content analysis was performed using thematic analysis in ATLAS.ti version 8.0. (ATLAS.ti, Bergmannstraße 68, Berlin, Germany). Demographic and self-reported clinical data were analyzed using descriptive statistics, such as frequencies, means, and percentages.

Results

Literature review

The 23 full-text articles reviewed yielded an initial conceptual model that included moderators, triggers, modifiers, treatment,

objective manifestations, subjective experiences, and impacts of MS spasticity (Table 1, Column 2; Supplemental Table 2) [10, 11].

Interviews with MS clinicians

The clinicians were two physicians and a physical therapist. They had an average of 22 years of experience treating PwMS. They reported PwMS using a wide variety of spasticity descriptors, including stiffness, spasms, muscle contractions, weakness, heaviness, tightness, and cramping. All clinicians described PwMS reporting pain as a part of the spasticity experience. The key revisions of the conceptual model based on the clinician interviews and the input of the multi-disciplinary experts on spasticity were the addition of: the triggers of physical dysfunction (e.g. skin lesions) and other environmental factors (e.g. tight clothing); altered voluntary movement pattern, which is an objective manifestation of spasticity in the final model; both slowness of movement and muscle jerks as subjective experiences in the final model; and the impact of loss of leisure and physical activities as a long-term consequence. Other key revisions include the removal of the descriptors of rigidity, limited range of motion, and orthopedic symptoms and the impact of disability (Table 1, Column 3; Supplemental Table 3).

Interviews with people with spasticity due to MS

Participant characteristics

Participants ($n=20$) had a mean age of 47.3 ± 9.6 years and were mostly female ($n=17$, 85%) and white ($n=16$, 80%) (Table 2). Sixty percent of participants reported their employment status as disabled, and 80% had at least some college education. Participants were diagnosed with MS for 11.6 ± 8.8 years. They reported experiencing spasticity for 12.3 ± 9.5 years, and their average spasticity NRS-S score was 5.4 (standard deviation = 1.6). Participants experienced spasticity in the legs ($n=19/20$, 95%), arms ($n=16/20$, 80%), feet or toes ($n=13/20$, 65%), fingers or hands ($n=10/20$, 50%), hips ($n=7/20$, 35%), and back ($n=4/20$, 20%). The most common current antispasticity treatments included stretching ($n=16/20$, 80%), oral baclofen ($n=12/20$, 60%), and massage ($n=11/20$, 55%).

The quantitative results and representative qualitative quotes from the interviews with PwMS are provided in Table 3. A summary of the concepts identified during this research at each step is listed in Supplemental Table 3. In this table, key changes are noted from each step of the model development.

Final conceptual model

The draft conceptual model based on the targeted literature review was modified by findings from the interviews of clinicians and people with spasticity due to MS and was finalized by the multidisciplinary experts on spasticity (Table 1 Column 4; Figure 2). The final conceptual model describes moderators (variables that affect the presentation of spasticity for PwMS), triggers, modifiers (descriptors of the experience of spasticity), and treatment of spasticity. These affect a range of objective manifestations and subjective experiences of MS spasticity. These subsequently result in physical impacts that can lead to functional limitations, social impacts, and emotional/psychological impacts. The conceptual model then describes the long-term consequences of spasticity, which may ultimately reduce the health-related quality of life of PwMS.

Table 1. Multistep process for developing the integrated conceptual model of multiple sclerosis spasticity^a.

Key concept	Step 1: Literature review	Step 2: Clinician Interviews N = 3	Step 3: Patient Interviews/ Final Conceptual Model ^b N = 20
Moderators			
Sex	✓	✓	✓
Age	✓	✓	✓
Duration of MS	✓	✓	✓
Type of MS	✓	✓	✓
Disability due to other underlying conditions		✓	✓
Other MS symptoms that may influence spasticity ^c	✓	✓	✓
Triggers			
Temperature/humidity	✓	✓	✓
Excessive physical activity			✓
Fatigue	✓ ^d	✓	✓
Stress	✓ ^d		✓
Other environmental factors			✓
Pain	✓	✓	✓
Physical dysfunction ^e		✓	✓
Infection	✓	✓	✓
Menstruation	✓	✓	✓
Objective manifestations			
Increased muscle tone (velocity dependent)	✓	✓	✓
Spasms	✓	✓	✓
Clonus	✓	✓	✓
Hyperreflexia	✓	✓	✓
Altered voluntary movement pattern		✓	✓
Subjective experience			
Spasms	✓	✓	✓
Tightness	✓	✓	✓
Pain	✓	✓	✓
Stiffness	✓	✓	✓
Difficulty moving or bending		✓	✓
Muscle cramping	✓	✓	✓
Weakness	✓ ^f	✓	✓
Heaviness		✓	✓
Muscle jerks		✓	✓
Slowness of movement		✓	✓
Muscle tension		✓	✓
Physical impacts			
Fatigue	✓	✓	✓
Limited range of motion	✓ ^g	✓	✓
Abnormal posture or gait		✓	✓
Bladder dysfunction	✓	✓	✓
Pain	✓	✓	✓
Sleep impairment		✓	✓
Functional limitations and impacts			
Daily activity/functioning impairment	✓	✓	✓
Walking impairment	✓	✓	✓
Balance impairment/postural instability	✓	✓	✓
Reduced dexterity	✓	✓	✓
Difficulty with transfers	✓ ^h	✓	✓
Reduced swallowing	✓	✓	✓
Sexual dysfunction	✓	✓	✓
Social impacts			
Reduced time with family and friends			✓
Work limitations		✓	✓
Emotional/psychological impacts			
Fear of falling		✓	✓
Frustration		✓	✓
Depression	✓	✓	✓
Anxiety	✓	✓	✓
Sense of helplessness	✓	✓	✓
Limited ability to relax		✓	✓
Embarrassment			✓
Long-term consequences			
Loss of driving ability		✓	✓
Falls/injuries	✓	✓	✓
Increased burden of care for ADL	✓	✓	✓
Loss of employment		✓	✓
Loss of mobility		✓	✓
Pressure injuries	✓	✓	✓

(Continued)

Table 1. Continued.

Key concept	Step 1: Literature review	Step 2: Clinician Interviews N=3	Step 3: Patient Interviews/ Final Conceptual Model ^b N=20
Loss of leisure and physical activities		✓	✓
Contractures	✓	✓	✓
Loss of independent living		✓	✓

Note: Abbreviation: ADL=activities of daily living.

^aAt each step of model development, six multidisciplinary experts on spasticity were consulted (JB, JRS, JMW, FB, MC, and EFF).

^bMultidisciplinary experts on spasticity were consulted, and some concepts were removed based on their feedback (see [Supplemental Table 3](#) for more detail).

^cOther MS symptoms included: increased disability/motor impairment, pain, musculoskeletal symptoms, orthopedic symptoms, urinary and bowel dysfunction, balance disorders, fatigue/deconditioning, weakness, ataxia, sensory abnormalities.

^dFatigue and stress were identified in the literature review only as impacts of spasticity.

^ePhysical dysfunction included gastrointestinal problems, such as constipation, and skin lesions.

^fWeakness was identified in the literature review only among other MS symptoms that may influence spasticity.

^gLimited range of motion was identified in the literature review as a descriptor of spasticity.

^h"Transfers" was identified in the literature review as an impact of spasticity.

Table 2. Demographic and self-reported clinical characteristics.

Characteristic	N=20
Age, years	
Mean ± SD	47.3 ± 9.6
Sex, n (%)	
Male	2 (10.0)
Female	17 (85.0)
Other	1 (5.0)
Ethnicity, n (%)	
Hispanic or Latino ethnicity	1 (5.0)
Not Hispanic or Latino	17 (85.0)
Missing	2 (10.0)
Race, n (%)	
White	16 (80.0)
Black or African American	3 (15.0)
Other ^a	1 (5.0)
Highest Level of Education, n (%)	
Secondary/high school	4 (20.0)
Some college	8 (40.0)
Four-year college degree	4 (20.0)
Postgraduate degree	3 (15.0)
Other ^b	1 (5.0)
Duration Since MS Symptoms First Noticed, years	
Mean ± SD	16.3 ± 11.1
Median (range)	16.0 (1.3-36.7)
Duration Since Spasticity First Experienced ^c , years	
Mean ± SD	12.3 ± 9.5
Median (range)	10.0 (0.6-36.7)
Self-Reported Duration Since MS Diagnosis, years	
Mean ± SD	11.6 ± 8.8
Median (range)	9.9 (1.3-36.0)
Current Treatment for Spasticity ^d , n (%)	
Stretching	16 (80.0)
Oral baclofen	12 (60.0)
Massage	11 (55.0)
Spasticity Numeric Rating Scale	
Mean (SD)	5.4 (1.6)
Median (range)	5.5 (3.0-8.0)
Patient Determined Disease Steps ^e , n (%)	
Normal (0)	0
Mild disability (1)	1 (5.0)
Moderate disability (2)	4 (20.0)
Gait disability (3)	3 (15.0)
Early cane (4)	3 (15.0)
Late cane (5)	0
Bilateral support (6)	4 (20.0)
Wheelchair/scooter (7)	4 (20.0)
Bedridden (8)	1 (5.0)

Note: Abbreviation: SD=standard deviation.

^aOther race: "mixed" (n=1).

^bOther education: "General Educational Development" (n=1).

^cOne patient had an incomplete date entered. It was set to missing.

^dNot mutually exclusive.

^eLearmonth et al. 2013 [9].

Discussion

Spasticity is common in PwMS, although difficult to characterize because it is complex and multidimensional. Our conceptual model, derived from this qualitative study, integrates a targeted literature review, clinician opinions, and insights from people with spasticity due to MS with opinions from experts in the field of MS spasticity, to provide a comprehensive framework to better describe and understand spasticity in PwMS.

The literature provided the information necessary to develop the initial draft of the conceptual model of MS spasticity. The key concepts obtained from the literature review included moderators of MS spasticity (duration of MS, age, sex, type of MS), triggers of spasticity, descriptors of spasticity, and impacts and consequences of spasticity ([Supplemental Table 2](#) and [Supplemental Table 3](#)) [4–6, 11–30]. The spasticity experts reviewed this information, and then the draft model was used to develop the interview guide used for clinician interviews.

The clinicians and multi-disciplinary experts gave us information that further refined the model. Two additional triggers were added: skin lesions and tight clothing. Their feedback also led us to remove rigidity and limited range of motion from the model. The following descriptors of spasticity were added based upon their feedback: weakness, slowness of movement, altered voluntary movement pattern, and muscle jerks. Disability was removed from impacts and consequences. Frustration, loss of mobility, difficulty with transfers, and reduced life expectancy were added to impacts and long-term consequences.

The PwMS confirmed many items, identified some new concepts, and recommended removal of some triggers. Specifically, the new concepts were social impacts of reduced time with family/friends and embarrassment. They also recommended adding triggers of stress, physical activity (e.g. movement daily activities, exertion, sitting/standing too long) and other environmental factors, and removing triggers of urinary tract infection, full bladder, and sleep.

In addition, spasticity can occur alongside other symptoms of MS [12], making it difficult for PwMS to distinguish between the variety of sensorimotor dysfunctions they experience and spasticity. For instance, a few participants mentioned tremor or numbness as part of their spasticity experience; however, this descriptor was not confirmed in the literature or by the multidisciplinary experts on spasticity as being associated with spasticity. The authors believe that participants were using "tremor" in a non-technical way to describe an aspect of their experience. For instance, it is possible that they were experiencing clonus, which

Table 3. Summary of interview information from PwMS.

Spasticity triggers ^a	Quantitative assessment	Qualitative representative quotes
Temperature or humidity	17/20 (85%) reported temperature (both hot and cold) or humidity as a trigger for spasticity	"Yeah. And I—to say I absolutely love the heat and I am a bikini advocate. Um, but this has been a bit of a stretch for me and that's when I just—it, it really—the heat does warrant how long I can enjoy. I mean there's no boating now. It's I'll watch you from the beach kind of thing. Um, but I definitely, um, think that it does impact me a little bit." "the cold definitely makes [spasticity] so much worse... the heat is not great either...but the cold makes it so much worse." "the quick weather changes is enough to just kind of give me a little kick me down." "Certain exercises where I've had PT and I'm trying to stretch it out, it just draws back up even tighter."
Physical activity	12/20 (60%) reported physical activity as a trigger for spasticity	"I think it just wears down my body overall. So, I mean I'm extremely fatigued. I have to be very careful about how I spend what energy I have. It makes me really fatigued and also, I think maybe since I was using those muscles more or something, they're more, more prone to have spasticity." "When I'm having chronic fatigue, then I have more issues with spasticity." "If I walked up the driveway too many times a day, I would be hunched over [from spasticity]... getting into the house, go lie down, and kick for a minute...."
Fatigue, exhaustion, or feeling tired	9/20 (45%) reported fatigue as a trigger for spasticity	"when I'm stressed out or I've done too much, that's when I get more spasms with my spasticity."
Stress	5/20 (25%) reported tension as a trigger for spasticity	Examples included loud sounds, atmospheric pressure, temperature changes
Other environmental factors	4/20 (20%) reported other environmental factors as a trigger for spasticity	
Pain	3/20 (15%) reported pain as a trigger for spasticity	"Because I think that if it's just not, like I was describing before, if it's something that's just not where it's just a spasm and it doesn't come with very much pain, it goes away quicker. If it's coupled with pain that makes it harder, more intense, then it lasts longer."
Physical dysfunction ^b	3/20 (15%) reported physical dysfunction as a trigger for spasticity	"Um, like I mean so I mentioned intestinal issues. So I recently—they sent me to the ER two separate times because of the pain involved in that. And I mean it just seemed like the pain—like the excruciating pain from my stomach, it seemed to—I don't know. My legs got worse and, you know, it just seemed more miserable."
Subjective experience ^c	Quantitative assessment	Qualitative representative quotes
Spasms	20/20 (100%) reported spasms Spasms most frequently occurred in the legs (n = 12/20, 60%).	Spasms were often described as "twitching," "jerking," "jumping," or "kicking." "Um, to me it's when my muscles twitch and that's what they do. Like my fingers will twitch. My toes will twitch. You can see in my arms and legs. You can literally see them to where it looks like, um, it's jumping inside. Like my arm may not actually move, but you can see the muscle, um, twitch in the arm. And then there's times where you can actually see the arm move, like, like someone is moving it, but it's not me. It—that's when it gets really bad."
Tightness	20/20 (100%) reported tightness	"Um, like, kind of like, um, I've got the tightest jeans on in the world and feel like I'm having to walk very carefully, you know. Like when I'm just trying to move it's just like everything is tightened up." "...tightness [was] in my knee, but I think stiffness would be more in my leg."
Pain	19/20 (95%) reported pain	"It's like a tightness that tightens up, it's almost like taking a rope and tying it around one of your limbs and just squeezing the rope." "If the spasm is coupled with pain...then it lasts longer." "I get a lot of spasms...and they burn and hurt really bad." "muscles are aching and so tight that you're just miserable... and it's hard to function and walk."
Stiffness	17/20 (85%) reported stiffness Most participants (n = 11/17, 65%) experienced stiffness in their legs, followed by their arms or hands (n = 4/17, 24%).	"Um, stiffness. It's almost like having rubber bands in your body parts that are over stretched and if you don't loosen them up, they're going to snap in half." "I function a lot slower...because I'm stiff or I can't move as quickly as somebody might want me to." "when I'm experiencing spasticity, I cannot bend the knee at all."
Difficult to move or bend	15/20 (75%) reported difficulty moving or bending	Muscle spasms were considered to be "like 'charley horse' spasms, or the inability to move...my leg."
Muscle cramping	10/20 (50%) reported muscle cramping	"So what I had to do was sit back down on the bed and try to like do a massage at that knotted-up muscle until such time as the muscle relaxed and then the pain of the charley horse went away, but during that time, I know 15 min probably doesn't sound like that long of a time, but when your muscle is cramping and you're in a huge amount of pain, it is a long time, so yeah."
Weakness	10/20 (50%) reported weakness	"And, um, but, uh, sometimes it hits me as weakness. Um, my—I'd describe it like this. Sometimes my muscles feel like spaghetti noodles, you know."
Heaviness	10/20 (50%) reported heaviness	"It's like they're like heavy like I can't—like the same—the place where my leg gets like I told you like a voodoo doll is getting stabbed and not—feels like that. It's just offline. Like as far as lifting up the leg to do whatever, but just on and that."
Muscle jerks	9/20 (45%) reported muscle jerks	Muscle jerks were described as causing "twitches, spasms, contracting, tapping, kicking, and shakes." "Or that's more when like the jerking—like my muscles sit there and like contract and keep going and my leg will start literally like jerking and—like you can look at the muscle and you can see the muscle twitching and stuff, and that has woken me up. That usually happens during the night when I'm sleeping." "when my legs shake, my whole leg shakes. When my arms shake, my whole arm shakes. It jerks, yeah, it's big jerks."
Slowness of movement	5/20 (25%) reported slowness of movement	"Or if somebody—you know, your daughter watching you get in the car. "Come on. Let's go." I just function a lot slower. And again if that's because I'm stiff or I can't move as quickly as somebody might want me to. That's, that's what causes anxiety, is that external, uh, thing."

(Continued)

Table 3. Continued.

Physical impacts of spasticity	Quantitative assessment	Qualitative representative quotes
Fatigue	14/20 (70%) reported fatigue as a physical impact of spasticity	"[fatigue from spasticity] will wipe me out...from 45 min to two hours...you're trying so hard to move and do normal everyday things."
Limited range of motion	12/20 (60%) reported limited range of motion as a physical impact of spasticity	"I've had severe cricks in my neck, which I can't really attribute to anything other than potential spasticity."
Abnormal posture or gait	10/20 (50%) reported abnormal posture or gait as a physical impact of spasticity	It seems like I'm a little bit more slumped over lately and I have a lot of back pain like in my side, in my ribs it hurts. I'm a leaning a little bit to the left side and I have a hard time coming back over to the right because that's all just tight, and I seem a little bit more slumped over and not as upright. I can't go back, you know, like a bridge, like we used to back in the day, like make a bridge with your body, arch your back, yeah. "I'm hunched over...getting into the house [and I need to] go lie down..." "you can feel it...twitching or tremoring when I do go [to the bathroom]."
Bladder dysfunction	9/20 (45%) reported bladder dysfunction, which was described as being unable to hold their bladder and difficulty urinating, as a physical impact of spasticity	
Pain	8/20 (40%) reported pain as a physical impact of spasticity	"It, well, it hurts, you know, it's like when you get a cramp, it hurts and then it hurts usually if I have one in my calves, sometimes they feel bad. My calves hurt several days after because it's been pushing, it spasms, yeah, I have it like three or four days after, like I've been working out but I haven't." "I'm in pain every single day. I have a pain in my hip, but I experience pain in other areas every single day...The spasticity will make the back pain worse from jerking." "I wake up from those full body jerks...and I toss and turn all night."
Sleep impairment	8/20 (40%) reported sleep impairment as a physical impact of spasticity 3/8 (38%) reported having difficulty falling asleep 3/8 (38%) reported being awakened after falling asleep	
Functional limitations/Impacts	Quantitative assessment	Qualitative representative quotes
Daily activity/functioning impairment	17/20 (85%) reported daily activity and functional impairments 8/17 (47%) reported difficulty carrying out housework, such as cooking and cleaning 4/17 (24%) found self-grooming difficult	"I'd be getting ready and if I had to shave my pits, um, I could lift my left arm and I could shave...but then if I had to lift my right arm I had to use my left arm to lift the right arm and then pin it on the wall in order to keep the arm up because it just wouldn't function." "if I have spasticity between the shoulder blades, my arms are just useless...I'm not going to be able to unload my dishwasher or do anything."
Walking impairment	16/20 (80%) reported walking impairment as a functional impact of spasticity	"You know, everything is just tight and so I can't, I can't undo my legs so that they will move. Um, I remember other times like walking and then you just stop because I can't—my hip and my upper thigh, thigh are too—so tight that I can't move at like a regular walk and I have to swing it around." "[it] feels like [my legs] get tightened...and it hurts to walk." Of the participants with balance impairment, most believed it was due to spasticity only.
Balance impairment/postural instability	16/20 (80%) reported balance impairment/postural instability as a functional impact of spasticity	Participants who struggled to walk because of spasticity reported this was due to muscle spasms and cramping in their lower extremities. "when your feet want to cramp up, and it can be like in the awkwardest of places, like it can be like the side of my ankle or something and it kind of turns my foot in a little bit, you know, it's hard to straighten out that foot and take a step or put your foot down flat because it just wants to bring it in."
Reduced dexterity	15/20 (75%) reported reduced dexterity as a functional impact of spasticity	"I can't reach and grasp things like I used to. They will slip out of my hand or my hand will get locked around it where I have to almost pry my fingers off of it."
Difficulty with transfers	14/20 (70%) reported difficulty with transfers as a functional impact of spasticity	e.g., getting in and out of the bed, the car, the tub, standing up from a seated position, and getting on and off the toilet "Oh, sometimes it's just a matter of, you know, I can't get in and out of my bed myself so he'll [help] me and sometimes just do it really. There are times that I've literally just gotten stuck because I can't get off the toilet so he'll help me with that."
Reduced swallowing	12/20 (60%) reported reduced swallowing as a functional impact of spasticity	"I have noticed it a couple of times. I have gotten choked up. And, um, like my drink actually—I had to spit it back out. And then, um, like as like swallowing certain pills, like I can't get those down." "it feels like muscle cramps in my throat... Sometimes it happens when I'm eating. Sometimes it happens when I'm swallowing."

(Continued)

Table 3. Continued.

Sexual dysfunction	5/20 (25%) reported sexual dysfunction which was related to pain from spasticity (3/5, 60%) and/or an inability to move their lower limbs (3/5, 60%)	...suddenly something that should have been so enjoyable was so painful and I couldn't move and I said, no, I need to stop now... And there was no being able to finish, no anything. It embarrassed me and made me feel awkward."
Social impacts	Quantitative assessment	Qualitative representative quotes
Reduced time with family/friends	14/20 (70%) reported that their spasticity has social impacts 6/14 reported that their spasticity (like pain, slowness of movement, or spasms) kept them from participating in social activities with family and friends)	"Um, it limits my ability to participate in social activities. And it also limits my ability in terms of scheduling because there are only certain parts of the day where I'm fairly sure that it's—I'm going to have less impact. So, for example, I don't typically schedule things early in the morning and I don't typically schedule things in the late afternoon or evening."
Work limitations	4/20 (20%) were employed at the time of the interview. 3/4 (75%) of those who were employed had work limitations due to spasticity	One had to modify the type of desk they used in the office and be more conscious of their slow movement while seated. Delegation of tasks to their employees when experiencing spasticity. Falling at work.
Emotional/Psychological impacts	Quantitative assessment	Qualitative representative quotes
Fear of falling	16/20 (80%) reported a fear of falling	"Yes, I do. That is a big fear of mine 'cause it, it has happened. Um, yeah. I mean it is—yeah. It's just one of my series of falls can result in injuries and I don't have time to be injured right now." One participant explained the concern that standing up after a fall could be daunting because their legs could stiffen or "lock up."
Frustration	14/20 (70%) reported frustration	"Just the spasms themselves. They're so frustrating when I can't stop them. If—I wish there was a medication that would—I could take during the day that wouldn't put me to sleep"
Depression	13/20 (65%) reported depression	"I mean it all over kind of could be depressive period, you know, because it limits your life in so many ways, like grandchildren, playing with your grandkids." "I went through a bad bout of depression... in December because my legs had gotten so bad that [I had] to lie around and everybody was out doing all the fun things."
Anxiety	13/20 (65%) reported anxiety	"Yeah. I think that's again when I can't get up from the floor or when I can't get into the car. Or here that's a good question. If there's other people around, right. And if I'm stuck on the floor and somebody wants to try to help me get up and I can't figure it out and my leg won't move, then that makes you feel anxious, right." "when I [have gotten] muscle cramps at night that wouldn't release, should I call 911?"
Sense of helplessness	10/20 (50%) reported a sense of helplessness	"Yeah, when they're happening, like I said, I can't use my right arm, so the thought of not being able to use your arm is a little discouraging and a little scary ...very much during you do feel helpless and you're like, oh my gosh, how long are these going to go on?"
Limited ability to relax	8/20 (40%) reported a limited ability to relax	"Yeah. Like still this right foot, I mean you can't—it's hard not to, um—like I'm focused on our interview, this interview. But a portion of my mind is still focused on what feels like that rock in the—in my foot...you can't fully relax when you're hurting." "[it's] difficult when it comes to relaxing because...my lower back... and my hip gives me trouble."
Embarrassment	3/20 (15%) reported embarrassment	"it's hard...when you have friends or family...that want to do things and I don't think my legs will let me do that."
Long-term consequences	Quantitative assessment	Qualitative representative quotes
Loss of driving ability	15/20 (75%) reported loss of driving ability as a long-term consequence of MSS	"Um, it's not, not great and it's not—in those moments, I try not to like drive at night...I get very, very achy and so I try to kind of keep it pretty simple." "Yeah, yeah. Yeah, it was, I loved driving but you know, when you get to the point you're afraid, you know, what if I kill somebody because I make a bad judgment call." "I can still drive, but I will not drive when I don't feel good. I won't put other people in danger."
Falls/injuries	14/20 (70%) reported falls/injuries as a long-term consequence of MSS	Have you...fallen as a result of your spasticity? "Yeah. I was carrying a bucket of potatoes that I was growing in a bucket and I fell in the grass and broke my—like the part of my left knee carrying." "I don't know if it was spasticity or imbalance. I don't know. I, I ended up falling down my stairs and I don't even know exactly what happened, but yeah, I fell down and broke my tailbone."
Increased burden of care for activities of daily living	12/20 (60%) reported increased burden of care as a long-term consequence of MSS	"Carrying certain things, sometimes getting up out of the chair or something, balancing myself sometimes, yeah, stuff like that." "Um, so stuff that would require me to move around a whole bunch or move around like say mowing the lawn or something like that, like there's no way I can do that. And so I do have to have my husband do that or different things like that. I couldn't go out and do that." "Um, sometimes I feel like I put too much on my husband. That crosses my mind. Um, I do worry about it."
Loss of employment	8/20 (40%) reported loss of employment as a long-term consequence of MSS	"I have not worked in over 10 years...the work limitations were not being able to walk up and down stairs...lift more than 10 pounds... stand for more than five minutes... sit for more than 10min without shifting position... I realize now that it was MS."

(Continued)

Table 3. Continued.

Loss of mobility	8/20 (40%) reported loss of mobility as a long-term consequence of MSS	"Well, right now I can't walk so yes, and it's not because of weakness or anything, it's because of spasticity that I cannot walk very well, because my knees will not straighten out." "Well I—yeah. I guess that's the whole walking. I just do thing—everything is slower. Um, I, I don't—I only use—in the house I have a three-wheeled walker, just to try to help me keep my head off the ground."
Pressure injuries	6/20 (30%) reported pressure injuries as a long-term consequence of MSS	"I had a stage 1 decub years ago on my foot, so I'm very cautious. Of course no matter how cautious you are, it can happen."
Loss of leisure activities/physical activities	5/20 (25%) reported that they had lost their ability to be physical active due to spasticity	"I like to go on long walks...and I've never been a very sportsy person, but like just doing different things like that and now I'm just thinking, oh gosh even a walk around my neighborhood is going to be very—it's painful. And so I do limit myself on different things like that because of it."
Contractures	4/20 (20%) reported contractures as a long-term consequence of MSS	"Yes. My right foot will turn inward. And the toes will also curl up."
Loss of independent living	3/20 (15%) reported loss of independent living as a long-term consequence of MSS	"Um, I have always been a really independent person. I have reached a point because of the fall risk, um, and my fatigue level, um, and my mobility issues, I can't do things like housework. So I can't vacuum. I can't, um, put groceries away. I can't do laundry. Things like that, I just, I can't do. I cannot independently live on my own and that, that is frustrating for me."

Notes: Abbreviations: ER=emergency room; MSS=multiple sclerosis spasticity; PT=physical therapy; PwMS=people with multiple sclerosis.

^aTwo spasticity triggers (infection and menstruation) were not specifically probed in the participant interview and were not mentioned by participants; however, they were endorsed by targeted literature search, clinician interviews and the spasticity expert input and were therefore kept in the final model.

^bIn the model, physical dysfunction includes gastrointestinal problems, such as constipation, and skin lesions.

^cMuscle tension was included in the final model based upon input received from the clinician interviews and the spasticity experts.

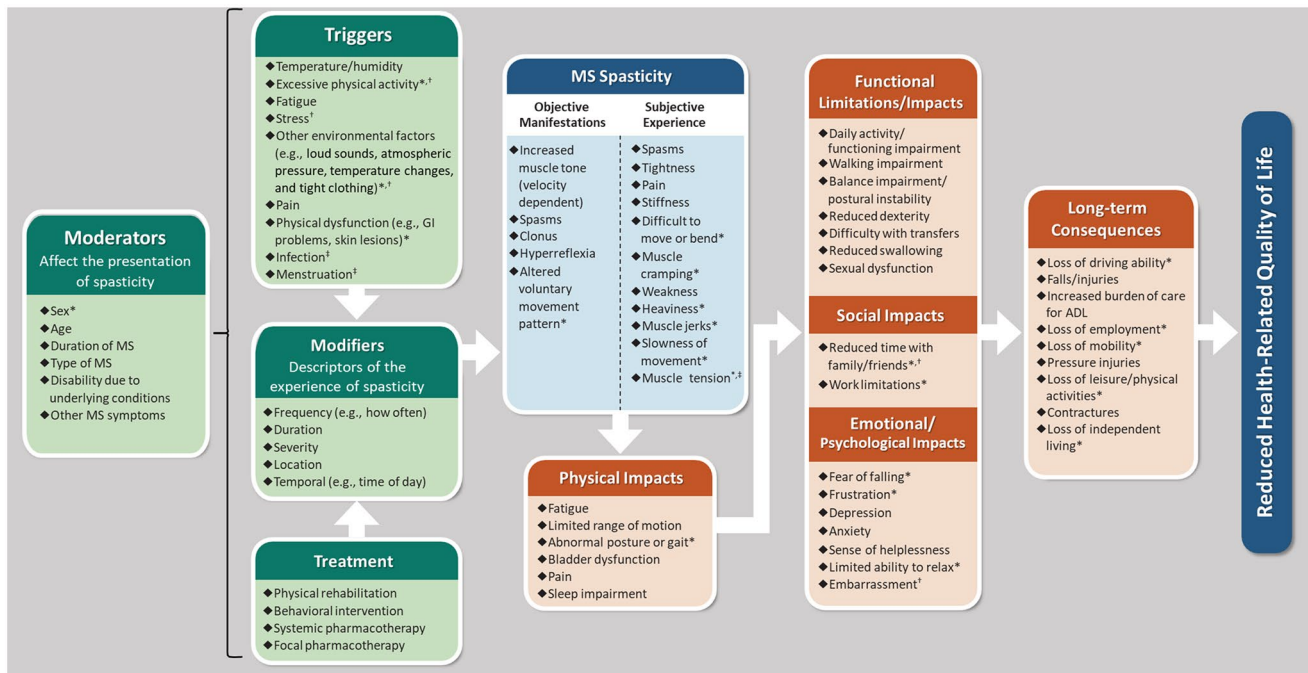


Figure 2. Integrated conceptual model of multiple sclerosis spasticity.

*Variable not identified in literature review.

[†]Variable not identified in clinician interviews.

[‡]Variable not identified in patient interviews.

Abbreviations: ADL=activities of daily living; GI=gastrointestinal; MS=multiple sclerosis.

Triggers, MS Spasticity - Subjective Experience, Functional Limitations/Impacts, Social Impacts, Emotional/Psychological Impacts, and Long-term Consequences are listed in order of decreasing percentage of patients reporting the variable, as in Table 3.

is a rhythmic movement commonly associated with spasticity. Weakness (subjective experience), bladder dysfunction (physical impact), and reduced swallowing (functional impact) were included in the conceptual model, as these items were associated with spasticity according to participants and the literature. The conceptual model includes moderators such as MS duration, type of MS, and other MS symptoms to acknowledge that there are external factors, both MS-related and non-related, that may influence the experience of spasticity.

This conceptual model presents pain as a prevalent and complicated component of spasticity; the recent literature [6, 28], opinions from clinicians and multidisciplinary experts on spasticity, and participant interviews confirmed pain as a subjective experience, a trigger, a physical impact, and a moderator of MS spasticity. Almost all participants reported pain as part of their spasticity experience. Clearly, understanding the relationship between pain and spasticity is important for optimizing the management of MS spasticity. Some patient participants felt that fatigue, which is one

of the most common and debilitating symptoms of MS [31, 32], could be caused by pain (subjective experience and physical impact) and soreness from spasticity. Thus, fatigue was included as both a trigger and physical impact of spasticity.

The long-term consequences of spasticity are difficult to assess with traditional clinical research studies, which usually last a maximum of two years; therefore, consequences beyond two years may not be well represented in the literature. However, PwMS described several long-term consequences of spasticity, including contractures, fear of falling, difficulty with transfers, loss of employment, loss of driving ability, loss of independent living, and increased burden of care. Given that PwMS may live decades with spasticity [33], additional research is needed to elucidate the long-term consequences of spasticity in order to develop and implement strategies to minimize their occurrence and improve the quality of life of PwMS.

This study had a number of strengths. Our model included multiple perspectives, including those of clinicians who treat many patients with MS spasticity and the expertise of people with the lived experience in an iterative process to develop this conceptual model of MS spasticity. During the iterative development process, experts from academia and industry further informed the development of the model. Importantly, the interviews with PwMS were repeated until saturation was reached. Another strength is that the project team utilized experts in conceptual models and qualitative research to conduct this project. This model confirms that MS spasticity is complex and multifaceted. The model takes a very complex experience and breaks it down into moderators, triggers, modifiers, and treatment of spasticity as well as describing spasticity (both objective and subjective experiences). In addition, this model describes the impacts and long-term consequences of spasticity that PwMS experience. The most comprehensive scale to date used to assess MS spasticity, the MSSS-88, focuses on the impacts of spasticity in PwMS but does not address moderators, modifiers, treatment, triggers, or long-term consequences of MS spasticity. [34].

The development of this conceptual model is not without limitations. Our initial literature review was not systematic and was time limited. However, this only served as a starting place for the iterative multistep model-building process. Some of the symptoms and consequences of spasticity described in our final model could also be explained by other symptoms of MS (e.g. difficulty moving that a PwMS attributes to spasticity may actually be related to muscle weakness). However, our approach balanced input from PwMS and clinicians to mitigate this limitation. Bias could have been introduced by financial compensation to the PwMS, although it was provided as reimbursement for their time at fair market value, as is standard in clinical research. Finally, all study participants being US based, and the sample of clinicians and PwMS was small. However, the demographics of our sample of 20 people with MS is similar to that of other studies [33, 35], and is in line with recent literature on qualitative concept elicitation, which indicates that a sample of 20 people should capture 97% of symptom concepts [36].

Conclusion

Spasticity in PwMS is common, complex, and has a wide range of moderators, triggers, modifiers, treatment, objective manifestations, and subjective experiences. MS spasticity can have impacts that are physical, functional, social, and psychological as well as long-term consequences that can ultimately reduce health-related quality of life. This integrated conceptual model of MS spasticity includes the

perspectives of PwMS, clinicians who treat PwMS, and multidisciplinary spasticity experts. The model may have several practical applications at the point of care, including improving clinician-patient dialogue, allowing treatment decisions to be personalized, assisting PwMS to set goals, and facilitating spasticity education. Furthermore, the model may be used to select and validate clinical research endpoints and to inform regulatory decision making.

Acknowledgements

Writing support was provided by Katie Crosslin, PhD and Stephen Gilliver, PhD, of Evidera/PPD.

Author contributions

Francois Bethoux, MD has received honoraria from GW Pharma, now a part of Jazz Pharmaceuticals, Inc. for participation in advisory board meetings; honoraria from Osmotica for consulting; and royalties from Springer International Publishing for being co-editor of a book.

Edelle Field-Fote, PT, PhD, FAPTA, FASIA serves as a paid consultant for Greenwich Biosciences, Inc., now a part of Jazz Pharmaceuticals, Inc.

William R. Lenderking, PhD, Katelyn N. Cutts, MS, and Erica Zaiser, PhD are employees of Evidera, which was contracted by Greenwich Biosciences, Inc., now a part of Jazz Pharmaceuticals, Inc. to perform this study.

Joanne Wagner, PT, PhD and Joris Berwaerts, MD are former employees of Greenwich Biosciences, Inc., now a part of Jazz Pharmaceuticals, Inc. Carlsbad, CA, USA.

Joshua R. Steinerman, MD is an employee of Jazz Pharmaceuticals, Inc., Philadelphia, PA, USA

Disclosure statement

Michelle Cameron, MD, PT, MCR serves as a paid consultant for Greenwich Biosciences, Inc., now a part of Jazz Pharmaceuticals, Inc.

Funding

The study and writing support were funded by Greenwich Biosciences, Inc., now a part of Jazz Pharmaceuticals, Inc.

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