Comprehensive Approach to Management of Multiple Sclerosis: Addressing Invisible Symptoms—A Narrative Review

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system, leading to neurodegeneration and manifesting as a variety of symptoms. These can include “invisible” symptoms, not externally evident to others, such as fatigue, mood disorders, cognitive impairments, pain, bladder/bowel dysfunction, sexual dysfunction, and vision changes. Invisible symptoms are highly prevalent in people living with MS, with multifactorial etiology and potential to impact the disease course. Patient experiences of these symptoms include both physical and psychosocial elements, which when unaddressed negatively influence many aspects of quality of life and perception of health. Despite the high impact on patient lives, gaps persist in awareness and management of these hidden symptoms. The healthcare provider and patient author experiences brought together here serve to raise the profile of invisible symptoms and review strategies for a team-based approach to comprehensive MS care. We summarize the current literature regarding the prevalence and etiology of invisible symptoms to convey the high likelihood that a person living with MS will contend with one or more of these concerns. We then explore how open communication between people living with MS and their care team, stigma mitigation, and shared decision-making are key to comprehensive management of invisible symptoms. We recommend validated screening tools and technological advancements that may be incorporated into MS care to regularly monitor these symptoms, offering insight into how healthcare providers can both educate and listen to patients, with the goal of improved patient quality of life. By pairing clinical knowledge with an understanding and consideration of the patient perspective, providers will be equipped to foster a patient-centered dialogue that encourages shared decision-making.

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**Graphical Plain Language Summary:**

Comprehensive Approach to Management of Multiple Sclerosis: Addressing Invisible Symptoms—A Narrative Review  
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The authors of this work include people living with MS and healthcare providers, working towards a common goal of raising awareness of the invisible symptoms of MS.

**What are the invisible symptoms of MS?**
People living with MS often experience ‘invisible symptoms’—symptoms which are not easily visible to others. These most frequently include:
- Fatigue
- Mood changes
- Cognitive changes
- Physical & emotional pain
- Bowel & bladder problems
- Sexual dysfunction
- Vision changes

**How can patients work together with providers to detect and monitor invisible symptoms?**
- Tell your MS care providers about all symptoms
- Discuss the routine use of screening tools
- Actively engage with your provider at all stages of care

**What can you do to manage invisible symptoms?**

**Maintenance of psychosocial well-being**
- Nurture relationships that support personal, spiritual, and emotional aspects of life
- Join peer support group(s) to normalize life with MS

**Preventative visits with primary care provider**
- Visit annually for prevention of problems
- Schedule additional visits as needed to manage risk factors, obesity, and obtain health screens

**Self-empowered choices which support health**
- Learn about invisible symptoms
- Maintain a nutritious diet
- Incorporate exercise/mindful movement into routine
- Quit smoking and limit sugary foods

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Keywords: Cognitive impairment; Fatigue; Invisible symptoms; Multiple sclerosis; Patient experience; Shared decision-making; Stigma

Key Summary Points

People living with multiple sclerosis (MS) experience many “invisible symptoms,” which are not uniformly recognized and addressed.

Invisible symptoms contribute to poorer quality of life for people living with MS due to their physical and psychosocial consequences.

Invisible symptoms can be assessed by incorporating screening tools into routine MS care and managed with both pharmacotherapy and alternative approaches.

Providers can empower people living with MS by open communication, efforts to mitigate stigma, and encouraging participation in shared decision-making for optimal outcomes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, graphical plain language summary, and video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14141120.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) in which the immune system attacks myelin sheaths, the insulating layer that forms around the nerves of the CNS, leading to the accumulation of nerve damage over time [1]. This neurodegeneration can lead to a variety of clinical symptoms that can vary from patient to patient. People living with MS and their care teams are generally well-versed in the symptoms of MS that are easily seen externally, such as difficulty walking, muscle spasms, or weakness. However, people living with MS experience many symptoms outside of obvious disability or other visible signs, which have been described as “invisible” symptoms due to their lack of external physical indicators. Commonly reported invisible symptoms can include, but are not limited to, fatigue, mood changes, cognitive changes, physical and emotional pain, spasticity, bowel/bladder dysfunction, sexual dysfunction, and vision changes [2, 3].

Invisible symptoms are common among people living with MS and may have a significant impact on their mental health, social roles/interactions, employment, daily living, and quality of life (QoL) [3]. They may also contribute more to patients’ perception of their health than visible symptoms of MS, and may cause reductions in QoL independent of Expanded Disability Status Scale (EDSS) and magnetic resonance imaging (MRI) changes [2, 4–7]. Despite their impact on QoL and high prevalence amongst people living with MS, awareness of these invisible symptoms remains low. Many people living with MS find that their invisible symptoms are dismissed by others, including family, colleagues, and healthcare providers (HCPs), because they visibly appear healthy [3]. Additionally, people living with MS may find certain invisible symptoms difficult to discuss with their provider, which can further hinder appropriate assessment and treatment of invisible symptoms [7–11]. When unaddressed, some symptoms may exacerbate one another and/or disease progression; for example, undertreated mental health conditions have been associated with disability progression [12]. In order to more consistently address invisible symptoms, new programs, such as the Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) program, hope to use technological advancements to capture information on invisible symptoms in routine MS care and subsequently provide standardized data across institutions to better inform
To further support comprehensive MS care and improve QoL for patients, there is a need to raise awareness of invisible symptoms [15, 16].

To begin addressing this need, this review draws on expertise and perspectives from clinical practice and the experience of our two patient authors, Cherie Binns RN, MSCN, and Keisha Currie MRC, CRC. Cherie Binns is a Registered Nurse (RN) and is also a Multiple Sclerosis Certified Nurse (MSCN); she was diagnosed with MS in 1994. Keisha Currie has a master’s degree in rehabilitation counseling (MRC), is a Certified Rehabilitation Counselor (CRC), and was diagnosed with MS in 2012. We summarize the current literature regarding the invisible symptoms of MS, with patient perspectives provided in Table 1.

### Table 1 Patient experiences with invisible symptoms

| Invisible symptoms     | Patient perspectives                                                                                                                                 |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Fatigue                | “I have experienced periods where my stress levels have been very high and my health was affected by it. I am less productive because of the pain and fatigue.” |
| Cognitive impairment   | “I sit down to call doctors’ offices…and have to ‘talk around’ an issue before the right words come to me. Wasted time and I feel like I sound stupid.”          |
|                        | “Cognitive impairment started with me playing mental word search, where I could not find the word but something close to it. Then, it moved to mental crossword, where I could describe everything about the word, i.e., it’s round, used in a game, but I could not find the word for ball.” |
| Pain                   | “Searing burn in my lower left leg. No one can see including me. So intense at times that I get distracted from what you are saying to me.”                        |
| Spasticity             | “One of the reasons I was sleeping so poorly was because I was in pain. I felt like I was on a spit roasting…I was in this cycle of poor sleep and pain for probably 3 or 4 years before we realized that it was spasticity that was causing the pain and waking me.” |
|                        | “One of the invisible symptoms that I have dealt with is involuntary muscle movements…that was one thing that was very hard to communicate to someone else.”        |
| Bladder/bowel dysfunction | “Losing control of my bladder/bowels in my 30s felt especially degrading. It was as if I was crossing a big line over into a new place.”                           |
| Vision                 | “Even without having optic neuritis, I just found out how my eyes are ‘aging’ faster than a person without MS…and in my case the color is changing. This has led me to have to wear glasses.” |
|                        | “I had lost so much [vision] that I could not drive for more than 2 years. A change in disease-modifying therapy, thankfully, helped me get workable vision back (some of it)…For me, I liken the brightness of the vision in my left eye to a night-light bulb, while the right eye looks like a 60-watt bulb.” |
| Sexual dysfunction     | “Kids are not here and we have had a lovely dinner out and a romantic movie. He is in the mood and mentally, so am I, but I cannot get physically aroused. He thinks I don’t love him as much anymore.” |
| Mood [36]              | “Sometimes, a [person living with MS] themselves does not realize their mood has changed, but those around them see it.”                                  |
|                        | “Living alone can allow symptoms to go unnoticed, causing a deeper dive into the depression.”                                                      |
|                        | “Fear of disease progression is also a concern.”                                                                                                   |
prevalence and etiology of invisible symptoms to convey the high likelihood that a person living with MS will contend with one or more of these concerns. We then explore how open communication between people living with MS and their care team, stigma mitigation, and shared decision-making are key to comprehensive management of invisible symptoms. We recommend screening tools and technological advancements to support these objectives, offering insight into how HCPs can both educate and listen to patients, with the goal of improved patient QoL. By pairing clinical knowledge with an understanding of the patient perspective, providers will be equipped to foster a patient-centered dialogue between MS care teams and people living with MS regarding invisible symptoms. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PREVALENCE, ETIOLOGY, AND CLINICAL COURSE IMPLICATIONS OF INVISIBLE SYMPTOMS

How Common are Invisible Symptoms in People Living with MS and How Do They Manifest?

A precise understanding of the prevalence of invisible symptoms in people living with MS remains elusive for many reasons, such as variable sample sizes between studies, the subjective nature of some symptoms, or the use of differing diagnostic/measurement tools. Here, we provide a brief overview of the prevalence of invisible symptoms of MS in the literature and share experiences from our patient authors on how invisible symptoms may manifest (Table 1).

MS fatigue is generally considered to be one of the most common invisible symptoms experienced by people living with MS. While the reported prevalence varies in the literature, approximately 80% of people living with MS may experience fatigue according to the National MS Society [17]. MS fatigue can include cognitive/mental, emotional, and physical components, although many patients who report fatigue are unaware of how encompassing it can be and report only the physical aspect of it. Cognitive fatigue is broadly defined as mental exhaustion after completing a task, while emotional fatigue refers to feeling emotionally overwhelmed or drained [18, 19]. Physical fatigue is characterized by a lack of physical energy which may limit mobility, participation in the community, and/or physical functioning [18, 19]. MS fatigue is often associated with sleep disorders; in a survey of 2375 people living with MS, 70% of respondents had at least one sleep disorder according to questionnaire responses [20]. Despite the high percentage of responses indicating a sleep disorder, only a small fraction of these individuals had been diagnosed by a physician [20]. Frequently overlooked sleep disorders in people living with MS include insomnia, restless leg syndrome, periodic limb movement disorders, and sleep-related breathing disorders [21]. Fatigue in people living with MS has psychosocial impacts, and has long been associated with depression and anxiety, both of which can involve sleep disruption as a symptom [22–24].

Mood and mental health disorders of many types are more prevalent in people living with MS as compared to the general population [25, 26]. A recent meta-analysis of 58 studies reported a prevalence of 30.5% for depression and 22.1% for anxiety in people living with MS [27], compared to 7% and 19%, respectively, in the general population [28]. Depression is frequently comorbid with anxiety, which in turn has been shown to be associated with suicidal ideation [29–33]. Despite the need to identify and address mood and mental health disorders, appropriate recognition and diagnosis can be complicated by other psychiatric comorbidities. For example, pseudobulbar affect (which may affect 10–46% of people living with MS), wherein people experience sudden, brief, exaggerated expressions of laughing or crying that may not match their actual mood, has distinct etiology from mood disorders but may result in similar symptom presentations [34, 35]. As
### Table 2 Common tools to screen for invisible symptoms

| Invisible symptom     | Screening tools                                                                 | Usage Notes                                                                                           |
|-----------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Fatigue               | Clinical interview                                                              | Assess at every visit                                                                                 |
|                       | FSS and ESS [117–119]                                                           | Comprehensive neuropsychological testing can be performed as indicated based on screening results and from the clinical history |
|                       | MFIS [120–122]                                                                  | Early baseline screening with SDMT or other validated screening tool followed by annual reassessment or more often as needed [129] |
| Cognitive impairment  | Clinical interview                                                              | The SILS measures word finding, vocabulary, and executive function for abstract thinking [124], while SDMT tests attention and speed of processing [125] |
|                       | SEFCI, which includes [123]:                                                     | The SDMT and CVLT-II have been utilized in remote testing of cognitive function [116]                  |
|                       | SHORT-D                                                                         |                                                                                                       |
|                       | SILS [124]                                                                      |                                                                                                       |
|                       | SDMT [125]                                                                      |                                                                                                       |
|                       | CVLT-II [126, 127]                                                              |                                                                                                       |
|                       | SLUMS [128]                                                                     |                                                                                                       |
| Pain                  | Clinical interview                                                              | Assess at every visit                                                                                 |
|                       | PDI [130]                                                                       |                                                                                                       |
| Bladder/bowel dysfunction | Clinical interview with specialist referral as needed                           | Assess at every visit                                                                                 |
|                       | MSQLI, which includes the BLCS and BWCS [110]                                   |                                                                                                       |
| Vision                | Snellen eye chart for visual acuity and color vision assessment                 | Assess at every visit                                                                                 |
|                       | OCT [131]                                                                       | See ophthalmologist for full exam every 1–2 years as indicated                                         |
|                       | LCVA, where possible [87]                                                       |                                                                                                       |
| Sexual dysfunction    | Clinical interview                                                              | Assess at every visit                                                                                 |
|                       | Refer to gynecology and/or urology as needed to assist with sexual dysfunction, address bladder problems, and to rule out other causes of sexual dysfunction |                                                                                                       |
| Mood                  | Clinical interview                                                              | Ask about and screen for mood changes at every visit                                                  |
|                       | PHQ-9 [132]                                                                     | Neuro-QoL annually                                                                                     |
|                       | GAD-7 [133]                                                                     |                                                                                                       |
|                       | BDI-II [134]                                                                    |                                                                                                       |
|                       | Neuro-QoL [111]                                                                  |                                                                                                       |

*BDI-II* Beck Depression Inventory-II, *BLCS* Bladder Control Scale, *BWCS* Bowel Control Scale, *CVLT-II* California Verbal Learning Test, Second Edition, *ESS* Epworth Sleepiness Scale, *FSS* Fatigue Severity Scale, *GAD-7* Generalized Anxiety Disorder Scale, *LCVA* low-contrast visual acuity, *MFIS* Modified Fatigue Impact Scale, *MSQLI* MS Quality of Life Inventory, *Neuro-QoL* Quality of Life in Neurological Disorders, *OCT* optical coherence tomography, *PDI* Pain Disability Index, *PHQ-9* Patient Health Questionnaire, *SDMT* Symbol Digit Modalities Test, *SEFCI* Screening Examination for Cognitive Impairment, *SHORT-D* Short Word List, *SILS* Shipley-2 Institute of Living Scale, *SLUMS* Saint Louis University Mental Status

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mood and mental health disorders are so often overlooked, yet are such a vital component of overall health, we address them in more detail in a companion review [36].

Cognitive impairments are reported to affect up to 70% of people living with MS; these impairments may include slowed cognitive processing speed, episodic memory decline, difficulties in executive function, verbal fluency changes, and reductions in visuospatial analysis [37, 38]. Such changes occur in the early stages of MS in 20–45% of cases and frequently are already present at the time of MS diagnosis [39–42]. Generally, in the early phases of MS, processing speed and executive functions are impaired, with changes in memory and attention beginning later in the disease course [42–44]. Patients may also experience a change in cognitive ability that does not meet the clinical threshold for impairment, but may still contribute to a reduced QoL [38, 45]. A systematic review of 12 studies examining employment for people living with MS found that individuals with MS who were unemployed or had reduced their working hours displayed poorer performance on cognitive tests than people living with MS who had not changed their employment status [46]. This is aligned with prior studies suggesting that people living with MS may leave the workforce early due to cognitive impairments and/or negative work events caused by them [47, 48]. Cognitive impairment is also an important concern for pediatric-onset MS (POMS); in a population-based longitudinal cohort study of the Swedish MS Registry, individuals with POMS had higher rates of cognitive decline as adults relative to those with adult-onset MS [49]. The cognitive impairments experienced by children and adolescents with POMS create a barrier to completing their education, which would have impacts well into adult life [50].

Pain prevalence rates in people living with MS vary widely in the literature, with estimates in the range of 29–86% [51–55]. Historically, pain was not considered a symptom of MS, but HCPs now recognize that pain exists for many individuals with MS and impacts many aspects of their lives [56]. A variety of pain types are associated with MS, including neuropathic pain, trigeminal neuralgia, burning limb pain, and musculoskeletal pain [51, 56, 57]. In a survey of 1865 MS outpatients, pain was documented as the top contributing symptom to a patient’s perception of health, followed by gait dysfunction and fatigue [4]. Pain has also long been known to worsen the mental health of people living with MS [9]. In the case of chronic pain, social functioning and mental health are more likely to be impaired among people living with MS, and the extent of impairment is associated with the severity of pain [10]. In a survey of participants in the North American Research Committee on Multiple Sclerosis registry, 65% of respondents indicated they would definitely or probably consider physician-assisted suicide if experiencing unbearable pain, demonstrating the impact of chronic pain on QoL and hopelessness, and the urgent need to address pain [58]. For some individuals with MS, pain may trigger or aggravate spasticity, which occurs in approximately 40% of people living with MS [59, 60]. Spasticity, defined as feelings of stiffness and/or involuntary muscle movements, may manifest within a wide range of severity [61]. People living with MS have reported that spasticity has negative impacts on their activities of daily living and QoL [60].

Bladder and bowel dysfunction is also frequently reported by people living with MS. At least 80% of people living with MS experience some degree of bladder dysfunction according to the National MS Society [62], which is approximately three times as common as that among the general population, in which the average prevalence of female urinary incontinence is 27.6% [63]. Common types of bladder dysfunction include increased frequency and/or urgency of urination, hesitancy in starting urination, higher frequency of nighttime urination, retention, and incontinence [62]. Untreated bladder problems can lead to worsening of other MS symptoms, increased risk of bladder or urinary tract infections, and reduced QoL [62, 64]. Bowel problems also may occur for people living with MS, with duration of disease and disability severity increasing the likelihood of experiencing symptoms [65, 66]. Approximately 50% of people living with MS experience neurogenic bowel dysfunction (fetal
incontinence and/or constipation), which may cause humiliation and distress [67, 68]. In addition to neurogenic bowel dysfunction, people living with MS may experience gastrointestinal disorders, although the connection between gastrointestinal disorders and MS requires further study [69]. In a survey of 6312 people living with MS, approximately 42% experienced gastrointestinal disorders, most commonly irritable bowel syndrome [70]. These gastrointestinal disorders are associated with lower physical and mental QoL [70].

According to the National MS Society, as many as 91% of men and 72% of women living with MS may experience sexual problems [71]. Prevalence rates for sexual problems vary in the literature, but are generally high, yet these symptoms have a high risk of undertreatment because HCPs frequently do not initiate conversations about this topic and patients do not always feel comfortable doing so themselves [72, 73]. Sexual dysfunction experienced by people living with MS can manifest in several different ways [74]. Men with MS are most likely to experience erectile dysfunction (50–75%), ejaculatory dysfunction and/or orgasmic dysfunction (50%), reduced libido (39%), and anorgasmia (37%) [75–77]. Frequently described types of sexual dysfunction in women are reduced libido (58–64%), anorgasmia (37–67%), and vaginal dryness with subsequent dyspareunia (23–52%) [74, 78–82].

Finally, vision problems are often experienced by people living with MS, with the most common concerns being reduced visual acuity, reduction in contrast sensitivity, changes to color vision, and ocular motility disorders [83, 84]. In a survey of 9107 respondents with MS in the North American Research Committee on Multiple Sclerosis registry, 60% of people reported some kind of vision problem on the Vision Performance Scale [85]. Inflammation of the optic nerve, known as optic neuritis, is cited as the first symptom of MS for approximately 20% of patients and occurs during the MS disease course in 50% of cases [86]. Vision problems are inversely correlated with health-related QoL in people living with MS, largely due to patients experiencing reductions in their general vision, lessened ability to do near and distance activities, limitations on their ability to fulfill roles in daily life, and decreased capacity to drive [84, 87, 88].

What Causes Invisible Symptoms?

The majority of these invisible symptoms are due to the lesions of MS. Some of these can be worsened for secondary and tertiary reasons such as a complication of a change that occurred due to a lesion or a psychosocial change. For example, fatigue is known to have multifactorial etiology, with “primary fatigue” deriving from lesions/inflammation in the CNS and their sequelae, and “secondary fatigue” arising due to other invisible symptoms, adverse effects of medication, and/or comorbid sleep disorders [24, 89, 90]. Fatigue may also be caused by other medical conditions, such as hypothyroidism, cardiopulmonary disease, or anemia; this confounds the identification of fatigue as a symptom of MS. For sexual dysfunction, these various contributions to etiology are formally categorized into “primary” factors (lesions in the neural pathways for sexual functions), “secondary” factors (muscle weakness, fatigue, and other MS symptoms), and “tertiary” factors (psychological influences such as altered self-esteem or changes to relationships, emotional factors, and cultural effects) [74].

Additionally, as some people living with MS describe their symptom clusters to providers, it may be apparent that in the individual, there is a “snowball effect” that compounds those complaints. For example, pain or urinary frequency can wake a person multiple times during the night, causing sleep to be interrupted and therefore adding to daytime fatigue. This fatigue may minimize the patient’s capacity to perform mindful movement/exercise, and subsequently pain increases the following night and a vicious cycle is set in motion.
Do Invisible Symptoms Impact Disease Course?

While there is not currently a clear consensus about the impact of invisible symptoms on disease course, there is increasing evidence to suggest that some may exacerbate disease progression. Stress may be associated with MS onset and relapse, with some studies suggesting a link between stress and an increase in lesion activity [91–93]. Additionally, a recent preclinical study in an animal model of MS examined metabolite changes following either physical or psychological stress [94]. The study found that oligodendrocytes in rats that experienced either type of stress prior to demyelination had altered levels of metabolites suggestive of changes in neuronal integrity/viability and cell membrane synthesis relative to unstressed controls [94]. The study found that oligodendrocytes in rats that experienced either type of stress prior to demyelination had altered levels of metabolites suggestive of changes in neuronal integrity/viability and cell membrane synthesis relative to unstressed controls [94].

Likewise, anxiety may be associated with an increased risk of disease activity, including relapses, disability worsening, and MRI activity [6]. Meanwhile, conflicting evidence exists regarding the potential impact of cognitive decline on disease course. Cognitive decline, which has been suggested to be strongly associated with cortical atrophy patterns, has been shown to be predictive of MS disease progression [95, 96]. Additionally, deep grey matter volume, diffusive changes in the thalamus, and hippocampal volume have been correlated with cognitive performance in several studies [97]. In a study of 46 people living with MS and 14 healthy controls, people living with MS experiencing cognitive fatigue had more relapses and developed more brain atrophy during 17 months of observation than did patients without cognitive fatigue [98]. However, cognitive fatigue may also be a consequence of brain atrophy, and is related to brain volume and lesion burden, confounding the understanding of a causative relationship [99, 100].

People living with MS have also referred to feedback loops in which unmitigated invisible symptoms promote disability severity/progression. A person living with MS may be experiencing depression/fatigue/social anxiety, and without proper support may have reduced motivation to exercise; subsequently, their weakness and gait impairment progress. In some cases, invisible symptoms accelerate disease progression, and yet disease progression can result in worsened invisible symptoms. Given this close relationship and possible feedback loop between disease progression and invisible symptoms, addressing invisible symptoms begins with a clinical interview that prompts the person living with MS with questions about such symptoms. Screening tools may then be used to gain more information about the patient’s experience. The clinical interview and screening process may also help determine whether the person living with MS should be referred to a specialist.
symptoms may have a synergistic outcome on MS disability outcomes. While the influence of invisible symptoms on disease progression requires further research, their impact on functional disability and QoL is evident.

HOW CAN WE AS A COMMUNITY ADDRESS INVISIBLE SYMPTOMS IN A COMPREHENSIVE MANNER?

Open Communication Between People Living with MS and Their Care Teams

Comprehensive management of invisible symptoms requires effective communication and trusting relationships between HCPs and patients. Issues of communication permeate the patient perspective of managing invisible symptoms. A recent meta-analysis assessing the notion of “invisibility” in relation to people’s lived experience of symptoms of MS showed that patients may experience difficulty discussing their symptoms, as they may feel misunderstood or invalidated when seeking care [3]. Additionally, patients may experience HCPs asserting that some invisible symptoms, such as depression or anxiety, are not their expertise, and therefore it is not under their purview to address these patient concerns.

I constantly feel like I am fighting some system or individual to get my medical needs met.
—Keisha Currie

HCPs should proactively ask their patients about invisible symptoms and mental health, as some patients may not describe the invisible symptoms they are experiencing without prompting. Sexual health, in particular, is a sensitive topic about which many patients would prefer that HCPs initiated conversations [73]. Some patients may not connect such invisible symptoms with their MS diagnosis and therefore do not bring the problems to their neurologist’s attention. Some aspects of normal aging and menopause both have symptoms similar to the invisible symptoms of MS, increasing the possibility that a symptom will be assumed to not be related to MS and thus
remain unaddressed [101]. Further, when patients describe their symptoms, HCPs should be aware that word choice may not fit neatly into medical definitions and should work to ensure that people living with MS are appropriately heard.

The clinical interview may be conceptualized as the initial step of a screening process, wherein the provider gathers qualitative information from the person living with MS. Strategies such as motivational interviewing may help to normalize invisible symptoms and create an environment where the patient feels comfortable opening up about difficult symptoms associated with MS [102]. Techniques to employ include the “RULE” principles: Resist the righting reflex, Understand your patient’s motivation, Listen to your patient, and Empower your patient [103]. These techniques can be paired with counseling techniques known as OARS: Open-ended questions, Affirmations, Reflective listening, and Summaries [103]. Taken together, these approaches can help to identify patient self-stigmatizing, self-doubt, and self-judging. HCPs should also guide patients on how to reach them when the patient has a concern or question and ensure the responsiveness of assistive staff.

Screening tools, paired with a detailed clinical interview, can be utilized to identify invisible symptoms in people living with MS; we recommend some validated screening tools in Table 2. Additional screening tools for MS symptom assessment are offered by the National MS Society [104]. Despite the availability of such screening tools, patients may find that HCPs diagnose/assess invisible symptoms with reservation, and assessment tools may not be used consistently.

Generally, there is a neurological exam performed, but it is subjective and by no means inclusive of invisible symptoms.

—Keisha Currie

Screening for invisible symptoms can allow for early implementation of interventions that can help improve QoL for people living with MS. For instance, upon identification of cognitive decline, techniques for remediating this at work (e.g., minimizing distractions in the work area, multi-tasking less frequently) improve productivity and give people living with MS a sense of control over cognitive fatigue [105]. QoL itself may be monitored in people living with MS by documenting patient-reported outcomes (PROs). PROs are useful for incorporating

Fig. 3 Recommended framework for healthy living with MS for improved QoL. People living with MS can actively engage in the management of their invisible symptoms by taking steps to support overall physical and emotional health.
patient experience into the assessment of disease status, rather than relying on MRI or neurological exam alone [14]. To that end, QoL has been proposed as important to monitor in addition to EDSS scores and MRI [106]. A widely used option is the Short Form 36 questionnaire (SF-36), which uses 36 questions to examine physical and social functioning, role limitations due to physical and emotional problems, bodily pain, general health perception, vitality, and mental health [107, 108]. Some other QoL assessment tools expand upon the SF-36, such as the MS Quality of Life-54 (MSQOL-54) and MS Quality of Life Inventory (MSQLI) [109, 110]. Recently, the Quality of Life in Neurological Disorders (Neuro-QoL) measurement system was developed to serve as a neurology-specific screening tool for QoL; it includes multiple physical, mental, and social health parameters relevant to individuals with neurological conditions [111, 112].

Regular screening to monitor invisible symptoms and QoL in people living with MS may become easier as technology-enabled assessments are integrated into clinical care. For example, the MS PATHS program uses an iPad-based device, called the Multiple Sclerosis Performance Test (MSPT), to collect assessments completed by patients that are standardized across ten healthcare institutions, which not only enables improved care of individuals, but also generates data for research [13]. The MSPT includes the Processing Speed Test (PST) for cognitive function, the Contrast Sensitivity Test (CST) for visual acuity, the Manual Dexterity Test (MDT) for upper extremity function, a patient history questionnaire, and the Neuro-QoL test [113, 114]. In an analysis of 8022 follow-up visits from 4199 patients in which the MSPT was integrated into visits, the tablet-based data collection resulted in more patients completing assessment and in a shorter time frame relative to analog methods, making it easier to incorporate these tests into care in spite of time constraints placed on HCPs [115]. Digitally administered tools also hold promise for use via telehealth, which has become important during the COVID-19 pandemic; early work seeking to validate remote use of the Symbol Digit Modalities Test (SDMT) and California Verbal Learning Test (CVLT-II) suggests that these tools may be effectively used remotely [116]. Such self-administered and/or remote technology-based screening tools are likely the future of invisible symptom monitoring, as they can help to streamline information collection, thus allowing more concerns to be addressed in a shorter amount of time during clinical visits.

As invisible symptoms play an outsized role in patient lives both clinically and socially, it is essential to incorporate regular monitoring of these symptoms into MS care. These screening tools can encourage more comprehensive conversations and open communication between the person living with MS and their HCPs. Further, these screening tools can help determine whether referral for additional testing with a specialist is needed. It is worth noting that administering screening tools does require time, and therefore providers may prioritize which tools to utilize based on the clinical interview and quality of the screen.

Mitigate Stigma

In addition to the difficulties of navigating the healthcare system, people living with MS may also deal with challenging decisions around invisible symptoms in their personal and professional lives. Many of these decisions are fueled by managing or avoiding stigma from colleagues, family members, friends, and even strangers. The fact that many MS symptoms are not visible can create an illusion that a person with MS is not sick, and individuals who are not visibly sick are often not perceived as deserving of the care and accommodations they need [135]. Examples of stigma encountered by people living with MS include presumptions from others that a person with a handicapped placard must always have a visible disability or be of a certain age, and misinterpreting MS-related sleep disorders/fatigue as choosing to make fewer household contributions. The paradox people living with MS face is that by disclosing their MS to someone, they are exposing themselves to stigmatization or over-sympathizing, but by opting not to disclose MS, people living with MS are at risk of going without helpful
support and/or accommodations. Opting not to disclose MS can exacerbate mental health concerns due to the internalization/suppression of symptoms and dealing with them alone. Individuals with MS experiencing higher rates of stigma may report higher rates of depression [136] and lower QoL [137]. Thus, people living with MS experience a “burden of choice” when managing the decision to disclose or not to disclose their MS and/or the invisible symptoms they experience [3, 138].

Every day you wake up and do an inventory of what body parts are functioning properly, first. Then, you decide if you are going to lie to yourself and others and say, “I’m fine,” when asked how you are doing because you know it is easier.
—Keisha Currie

This decision may be particularly difficult to navigate in the workplace, where issues of stigma from supervisors/colleagues may collide with a patient’s health concerns [139–142]. Therefore, it can be beneficial for people living with MS to speak with a vocational or rehabilitation counselor about what is disclosed to an employer. Stigma can even be experienced in healthcare settings; people living with MS may encounter assumptions of drug-seeking behavior when trying to address pain.

As an administrator of a 35,000-member online group of people living with MS, I often hear, “We are not taken seriously!”, “I am treated as a drug seeker,” and “The doctor doesn’t believe me because they can’t see how this impacts me because I look good during the visit.”
—Cherie Binns

Given that patients are likely to encounter judgment from those not knowledgeable about MS and invisible symptoms, HCPs should discuss stigma mitigation strategies with their patients. Building networks of trusted friends and family can help alleviate both stigma and social isolation experienced by people living with MS [143]. Support groups affiliated with an MS center or on social media can help to normalize and legitimate the experiences of people living with MS [144]. Family support, or lack thereof, is also an important consideration for the burden of disease brought on by both invisible symptoms and mental health issues in MS. Those with a strong support system can include family members in the management of invisible symptoms, for example by guiding their family members in how to recognize MS fatigue and how to help [145]. Education of family members can be facilitated by using visual aids such as educational pamphlets, explaining symptoms with relevant specific examples, or holding moderated discussions with family and partners to assist in sharing and validating the patient’s views and experiences [146].

HCPs should also keep in mind cultural and societal issues that may contribute to stigma and stress in patients’ lives [147].

Often, African Americans have religious views and will reply, “Just pray about it!” to imply that God will simply take my MS away. Thankfully, I had developed my own views about this shortly after diagnosis or it would have been more isolating.
—Keisha Currie

People living with MS from minority backgrounds not only experience the general stigma encountered by MS patients of other races, but also are more likely to have an inherent distrust of the medical system due to racial bias encountered in healthcare, have religious views that influence decision-making, encounter language barriers during clinical visits, and/or have lower socioeconomic/educational status [148]. HCPs should consider the needs of minority communities when designing educational events and tools aimed at stigma mitigation. Customize the topics discussed for the specific audience, provide simple access to events (e.g., scheduled at times compatible with a variety of work schedules), and share offerings in multiple languages when appropriate [149].

Shared Decision-Making

The concept of shared decision-making has been growing in recent years across healthcare in general. Since MS is a preference-sensitive
condition, shared decision-making is of particular importance to achieve optimal patient care and satisfaction [150]. Patients who feel they are making care decisions together with their providers have been shown to have higher satisfaction with their treatment [151, 152]. Effective shared decision-making involves HCPs engaging patients in their care, taking the time to compare treatment options with the patient, learning what matters to their patient, and ultimately coming to a satisfactory decision as a team [150, 153].

I feel that HCPs can have honest conversations with patients about how their MS is presenting, how management strategies can be beneficial, and long-term planning. —Keisha Currie

To achieve such honest conversations, both patients and providers may take steps to actively participate in the management process and educate each other about invisible symptoms.

Provider Perspectives

As discussed earlier, establishing open communication and listening to patients’ experiences of invisible symptoms is an important step in achieving shared decision-making and equipping HCPs with a better understanding of patient QoL. Figure 1 summarizes how the routine use of screening tools can encourage open communication and help determine whether referral to a specialist is needed (Fig. 1). HCPs should also keep in mind that invisible symptoms may be more distressing to patients than the visible symptoms of MS or potential side effects of medication [2, 4]. Indeed, changes in abilities and the resulting QoL reduction can create periods in patient lives similar to grieving [36]. A component of this impact may derive from the psychosocial consequences of stigma patients experience around their invisible symptoms. Thus, providers should focus on their patient’s experience of which invisible symptoms and/or side effects are more or less difficult to live with, rather than making assumptions; an example of this interaction is provided in Fig. 2.

HCPs can begin the shared decision-making process by educating their patients on basic guidelines for healthy lifestyle habits and self-empowerment that can improve invisible symptoms, summarized in Fig. 3. Both non-pharmacological and pharmacological strategies for symptom management may be considered when deciding on an approach in partnership with patients; specific symptom management options and considerations for implementation have been reviewed previously [154–156]. Frequently utilized pharmacological options are also summarized by the National MS Society [157]. Common examples of non-pharmacological ways to manage these symptoms may include bladder/pelvic training with a physical therapist, dietary adjustments, exercise, meditation, music therapy, and/or support groups. For example, non-pharmacological treatments including exercise and cognitive training may improve patients’ cognitive function at relatively low cost and with minimal side effects [158]. Likewise, energy conservation training with an occupational therapist and cognitive rehabilitation therapy with an occupational/speech therapist or neuropsychologist may also provide benefits for managing these symptoms [159, 160]. Cognitive behavioral therapy has also been suggested to be effective in managing a variety of invisible symptoms, such as insomnia and pain [161, 162], and has the potential to maintain effectiveness when administered digitally as well [163]. In the case of sexual dysfunction, the type of dysfunction should be considered to appropriately guide patients. For example, sensory changes can be addressed by recommending different forms of stimulus, dryness can be managed with lubricants, and libido can be increased by working to manage other symptoms (e.g., depression, bowel/bladder changes, fatigue) [73, 164]. When pharmacotherapy is warranted, many symptoms including bladder spasticity/retention, bowel problems (irritable bowel syndrome/constipation), fatigue, cognitive decline (attention deficit, specifically), depression, headaches, sexual dysfunction, and paresthesia/pain can be effectively managed with
medications apart from MS disease-modifying therapy [31, 164–167].

Pain management requires special attention, as HCPs need to carefully consider the addictive potential of opioid and non-opioid therapies (e.g., gabapentin) and issues of drug accessibility, and need to consider alternative approaches [168, 169]. People living with MS are often interested in considering holistic approaches to pain management, such as mindfulness, yoga, or music therapy [170]. Non-pharmacological approaches may lead to clinically meaningful reductions in pain interference scores [171], and mindfulness meditation has been shown to be effective for pain reduction even during the administration of an opioid antagonist, suggesting a combination of mindfulness and pharmacotherapy may be particularly effective for pain management [172]. For individuals where pain medication is needed, HCPs and patients should set shared goals and discuss choice of medication, duration of use, and potential management of side effects [173].

Patient Perspectives

Just as providers should listen to patients’ experiences of invisible symptoms as part of the shared decision-making process, patients can participate in this process by openly describing all symptoms to their provider, sharing priorities regarding treatment options, and actively engaging in the management of their invisible symptoms. In doing so, people living with MS can inform providers about their unique experience and learn the self-management strategies that work well for them [174]. This involves implementing tactics that maintain overall health and support well-being, including attending regular preventive medical visits (Fig. 3). People living with MS can also take steps to maintain their psychosocial well-being by seeking out social supports that enhance stigma mitigation (Fig. 3). Through self-empowered choices, such as incorporating an exercise regimen tailored to their individual preferences, people living with MS can support their specific health needs (Fig. 3).

Patients can utilize various tools to track their symptoms, increase the odds of obtaining care for their invisible symptoms, and facilitate discussions with HCPs. Arriving at appointments with notes of items to discuss can increase the likelihood that all concerns are addressed. People living with MS can use a journal or mobile applications ("apps") to document symptoms between appointments, keep notes, and share information with their care team. Apps have become increasingly sophisticated and specialized in recent years, with options available not only to monitor symptoms but to manage them as well [175–177]. Some apps are dedicated to specific invisible symptoms, such as fatigue (MS Energise) or cognition (NeuroNation) [175]. Personal fitness trackers may also be useful for monitoring activity levels and planning wellness practices. Such technology can assist people living with MS in providing data to the HCP that will allow the MS care team to arrive at conclusions about invisible symptoms based on the patients’ day-to-day realities. HCPs may also use insights gained from this external data to engage in discussions with the person living with MS as part of the shared decision-making process.

Online resources are also available to guide patients as they educate themselves about managing their invisible symptoms. For example, the organization Overcoming Multiple Sclerosis offers tools to inform both patients and providers about MS, including guides and resources for implementing lifestyle changes (e.g., recipes, guided meditations, and exercises) and community-building opportunities [178]. Many patient advocacy groups, such as the National MS Society, also offer resources online to support both people living with MS and their families [179]. Providers may share these resources with their patients to increase the patient’s self-efficacy and empower them to improve their QoL.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this review, we sought to raise the profile of invisible symptoms and explore a holistic
approach for MS care teams to effectively identify and manage them. There is a high likelihood that people living with MS are experiencing invisible symptoms, and when unaddressed, these symptoms have a detrimental effect on other symptoms of MS and on QoL. Invisible symptoms can have long-lasting impacts on a patient’s mental health, relationships, and career, due not only to the physical pain/discomfort that they cause, but also to their associated social stigma. Therefore, HCPs may consider proactively discussing invisible symptoms with patients and routinely utilizing screening tools. These actions signal to patients that the invisible symptoms they are experiencing are a normal component of life with MS and aid in the de-stigmatization of seeking care. When invisible symptoms are identified, HCPs may monitor them, discuss management options, and refer to an appropriate specialist as needed. Members of the care team should be aligned in the understanding that each patient is unique and must be sincerely listened to in order to ensure they have the support that they need/desire.

Empowering patients and providers alike to address the impact of invisible symptoms on overall QoL, and possibly disease progression, begins with increasing knowledge and closing communication gaps. A team-based, shared decision-making approach to MS care can unite people living with MS and their HCPs as they strive to accomplish those shared objectives. Due to the many stressors inherent in living with MS, this comprehensive care paradigm should include mental health professionals when an interdisciplinary team is needed, which we further explore in a companion review of mental health and MS [36]. By working to build trusting relationships between all members of the MS care team, HCPs can increase the odds of effective shared decision-making with their patients. Apps, digital guides, and online support groups can also serve as useful resources for managing invisible symptoms and building community—and can be as simple as using one’s phone, and seeking out specialist care as needed. By giving a voice to patients’ concerns and supporting the ongoing development of innovative ways HCPs can appropriately address invisible symptoms, MS care teams can offer people living with MS the best chance for maintaining a high QoL.

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