



# Case Study of an Adolescent Young Adult Patient With Multiple Sclerosis and Unpredictable Fatigue

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Female adolescent young adult patients who received a diagnosis of multiple sclerosis (MS) often experience unpredictable symptoms. Ineffective control of MS-related symptoms can adversely impact the quality of life of patients affected with MS. In this case study, we describe (a) a female adolescent young adult with unpredictable fatigue symptoms, (b) the pathophysiology of MS-related fatigue, (c) the National MS Society–recommended practice guidelines for fatigue, (d) current recommendations for pharmacology management of fatigue, and (e) stressors of patients with MS and their family caregivers. We propose that the use of multiple symptom-control interventions has the potential to promote quality of life and decrease suffering associated with unpredictable symptoms of MS.

## KEY WORDS

chronic illness, fatigue, multiple sclerosis, palliative care, symptom management, unpredictable fatigue

Multiple sclerosis (MS) is one of the most common chronic neurologic diseases in the United States, affecting approximately 1 in every 1000 young adults, or 2.3 million people worldwide,<sup>1</sup> and occurs more than twice as often in women compared with men. The

onset of MS usually occurs in young adults between 20 and 40 years, and there is no cure.<sup>1,2,4</sup> Individuals with MS typically experience unpredictable episodes of neurological-related symptoms and chronic fatigue.<sup>1,3</sup>

Multiple sclerosis is a demyelinating disorder of the central nervous system (brain and spinal cord), in which progressive demyelination, axonal loss, and neural degeneration lead to functional disability.<sup>1,2</sup> The prognosis for patients with MS is expected to be favorable for those who receive recommended disease-modifying treatments and do not display disease progression.<sup>3,4</sup> Multiple sclerosis symptoms include fatigue,<sup>5</sup> depression, memory impairment,<sup>4</sup> pain, blurred vision, diplopia, vertigo and dizziness, and limb weakness.<sup>3</sup> People with MS commonly report that fatigue adversely and often unexpectedly impacts their general physical functioning and quality of life.<sup>3-6</sup>

## SIGNIFICANCE

According to the National MS Society (NMSS), approximately 90% of patients with MS experience fatigue as their initial distressing symptom.<sup>4</sup> Both the cause and consequences of MS fatigue are considered multidimensional<sup>3</sup> and necessitate multidisciplinary treatment for successful symptom management.<sup>3,6,7</sup> Fatigue is defined as “a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.”<sup>6</sup> While many people with other chronic illnesses experience fatigue (eg, cancer, human immunodeficiency virus), MS-related fatigue differs from these because of its neurological/immunological aspects.<sup>8</sup> The definitive cause of fatigue in MS is currently unknown; however, it is postulated that MS-related fatigue may result from centrally mediated processes characterized by MS itself, such as demyelination and axonal loss in the central nervous system or immune actions.<sup>8,9</sup> To date, there are no evidence-based guidelines to treat fatigue effectively among individuals with MS. Furthermore, symptoms such as fatigue may be “hidden,” making it more difficult for the clinician to assess.<sup>4,5</sup> Therefore, it is especially important to have a way to assess and manage fatigue for persons with MS.

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## Purpose

The following case report describes a female adolescent young adult with a diagnosis of MS. In this case presentation, we describe her history of MS-related symptom of fatigue and how this symptom was perceived to adversely impact her quality of life.

## Case Presentation

A female adolescent young adult, aged 25 years, with a history of relapsing-remitting MS is the focus of the case study. For this presentation, we will use the pseudonym Ms X. This case presentation includes a discussion of the unpredictable and challenging nature of the symptom of fatigue and the complexity of managing it effectively.

In 2008, at age 22 years, Ms X. received a diagnosis of MS. At the time of diagnosis, Ms X. shared with her health care providers that she was experiencing episodes of unpredictable symptoms impacting her daily activities and quality of life. For instance, she reported her apprehension about experiencing significant fatigue while taking a shower and simultaneously experiencing numbness sensations “around and below her neck area.” She also shared concerns about the memory of her first MS-related symptom that included loss of vision in her right eye and experiencing unpredictable and frequent falls.

In an effort to control and manage the troubling and unpredictable symptoms experienced by Ms X., her health care providers prescribed glatiramer acetate (Copaxone), a disease-modifying medication for MS, and modafinil (Provigil) (Table) for fatigue. Ms X. described unexpected

numbness sensations in her right leg, which contributed to an inability to walk independently. She needed to receive physical therapy for approximately 6 months to relearn to walk. Following physical therapy, Ms X. continued to report unexpected episodes of falls and balance problems when attempting to walk independently. She described ongoing weakness in both legs that felt like having “cement bags being carried” on both legs and extreme fatigue.

Ms X. shared that her fatigue symptoms seemed to worsen during the first year after exposure to heat. The fatigue symptoms interfered with her ability to partake in daily activities and goals, which subsequently impacted her independence and quality of life. For example, she shared that she participates in an annual MS Challenge Walk program in her community. During this program, she walks 50 miles over 3 days, stating, “As long as I can put one foot in front of the other, that’s all I need, but that’s what it comes down to.”

## PHYSIOLOGY AND PHARMACOLOGY

Fatigue is categorized into primary and secondary forms, which are often difficult to differentiate.<sup>11-14</sup> Primarily fatigue can directly result from MS neuropathology due to demyelination of neural pathways affecting central domain, norepinephrine, or sympathetic adrenergic functioning.<sup>14,15</sup> Secondary fatigue can follow from a number of common comorbidities, including the neurovegetative effects of depression, medication adverse effects (such as those of central nervous system muscle relaxants such as baclofen

**TABLE Recommended Pharmacotherapy for Multiple Sclerosis Fatigue<sup>1,10</sup>**

Agent	Recommended Dosing	Comments
Amantadine (Symmetrel)	100 mg twice daily in morning and early afternoon	Antiviral agent. Exact MOA for treatment of multiple sclerosis fatigue is unknown but may potentiate central nervous system dopamine and norepinephrine pathways. Common adverse reactions include dizziness, anxiety, impaired coordination, and insomnia.
Modafinil (Provigil)	100 mg twice daily in morning and early afternoon/200 mg daily in morning	Schedule IV controlled substance. Stimulant medication FDA approved for treatment of narcolepsy. Exact MOA is unknown but may stimulate the $\alpha$ -adrenergic system or stimulate the hippocampus, the centrolateral nucleus of the thalamus, and the central nucleus of the amygdala. Common adverse reactions include headache, nausea and vomiting, anxiety, and insomnia.
Methylphenidate HCL (Ritalin)	10-20 mg twice daily in the morning and early afternoon	Schedule II controlled substance (central nervous system stimulant). Treat attention-deficit/hyperactivity disorder and narcolepsy. Blocks dopamine uptake to central adrenergic neurons, increasing sympathomimetic activity. More adverse reactions reported than with amantadine or modafinil. Common adverse reactions include anxiety, insomnia, nausea and vomiting, appetite changes, weight loss, and abdominal pain.

Abbreviations: FDA, Food and Drug Administration; MOA, mechanism of action.



and tizanidine), pain, psychosocial stress, and primary sleep disorders such as obstructive sleep apnea, periodic limb movement syndrome, or restless leg syndrome.<sup>11,12</sup> Fatigue also carries a long differential of other potential causes, including depression, cognitive impairment, sleep disorders, anemia, vitamin B<sub>12</sub> deficiency, heart failure, chronic obstructive pulmonary disease, hypothyroidism, diabetes, pregnancy, and chronic viral infections.<sup>11</sup>

Multiple sclerosis-related fatigue can have a modifying effect on other existing MS-related symptoms, including spasticity, neurogenic pain, coordination, ambulation, and vision.<sup>1-5</sup> For example, a patient with preexisting spasticity in the lower extremities and visual symptoms may experience temporary episodes of worsening of “shaky” or “blurry” vision,<sup>5</sup> as well as a sense of increased tightness and aching pain in the legs during periods of elevated physical fatigue.<sup>1-4</sup> Similarly, a patient with baseline balance problems and gait ataxia may experience a worsening of these problems with fatigue and may be at a heightened risk of falling during these periods. Finally, periods of heightened fatigue can contribute to a worsening of real-time cognitive functioning in individuals with existing MS-related cognitive deficits, leading to a temporary worsening in perceived cognitive performance, which could potentially impact work performance and/or social functioning.<sup>3-7</sup>

The pathophysiology of MS-related fatigue is incompletely understood but involves dysfunction in multiple brain regions including the primary motor cortex, the left superior frontal gyrus, the bilateral frontal gyrus, the inferior parietal gyrus, the thalamus, and the hypothalamic-pituitary-adrenergic (HPA) axis.<sup>10</sup> Associations have been established between MS-related fatigue, abnormal activation patterns, and axonal atrophy in these regions. Derache et al<sup>8</sup> found that MS patients with fatigue have reduced motor cortex inhibition, an abnormality that has also been found in amyotrophic lateral sclerosis, Parkinson disease, and stroke. Hanken et al<sup>9</sup> have found associations between fatigue and right parietal-temporal lesion burden and with gray matter atrophy in the left superior frontal gyrus and bilateral frontal gyrus, findings also observed by Derache et al.<sup>8</sup> These regions are known to contribute to attention and other related cognitive processes. Hanken et al<sup>9</sup> also found associations between fatigue and atrophy of the thalamus, putamen, caudate, superior frontal gyrus, and inferior parietal gyrus. More recently, Derache et al<sup>8</sup> found abnormalities in hypothalamic pathways related to MS fatigue.

Significantly elevated adrenocorticotrophic hormone levels indicating dysregulation of the HPA axis have been associated with MS-related fatigue.<sup>10</sup> The linkage between HPA axis dysfunction and proinflammatory cytokines in many chronic diseases, including cancer, has prompted research into relationships with MS fatigue with conflicting

findings.<sup>12-15</sup> In addition, associations between fatigue in impaired sympathetic vasomotor dysfunction have been demonstrated by some studies<sup>8,9</sup> but contradicted by others.<sup>5</sup>

### Fatigue Assessment

Currently, there are several established measurement scales with strong psychometric properties that investigators can review when planning to select self-report measures that are focused on fatigue and quality of life among adults with MS. Selection of measures that include a minimum number of items to reduce the risk of subject burden experienced by the target population is an important consideration when selecting self-report symptom measures for individuals with MS with unpredictable fatigue symptoms. We have included a list of fatigue assessment scales with established psychometric properties that are also viewed as concise in terms of number of items to review and complete by adults with MS and fatigue symptoms. Fatigue scales currently available include (a) 21-item Modified Fatigue Impact Scale<sup>13</sup>; (b) 5-item Multiple Sclerosis Quality of Life Inventory; (c) 14-item MS Self-efficacy Scale; (d) Fatigue Severity Scale,<sup>6</sup> and NIH PROMIS Fatigue scale. However, the 21-item Modified Fatigue Impact Scale has been recommended to measure fatigue associated with a diagnosis of MS by the Multiple Sclerosis Council for Clinical Practice Guidelines to measure the individual's perception of experienced fatigue during the previous 4 weeks.<sup>10</sup>

### National MS Guidelines for Management of MS-Related Fatigue

The National Multiple Sclerosis Society has established practice guidelines for the management of fatigue, which follow a 4-step process (Figure).<sup>10</sup> The first recommended step is to manage any medical or psychiatric conditions, such as depression, anemia, cognitive impairment, sleep

- Optimize management of “secondary fatigue” (e.g., caused by general medical conditions).
- Assess psychiatric conditions contributing to MS symptoms.
- Use behavioral management (rehabilitation).
- Use pharmacotherapy such as amantadine and modafinil.
- Conserve energy through proper exercise and rest-to-activity ratio.
- Employ assistive devices and environmental modifications.
- Use sleep hygiene and stress reduction training.

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**FIGURE.** Management of multiple sclerosis-related fatigue.



disorders, or medication adverse reactions, which may contribute to fatigue. The second step is to manage any MS symptom that may contribute to fatigue such as weakness, spasticity, and ataxia. The third step is focused on implementing behavioral-management interventions, such as sleep hygiene, energy conservation, and stress reduction. The fourth step includes the use of pharmacotherapy when behavior management approaches are not effective or are viewed as resulting in suboptimal outcomes.

### Pharmacology Recommendations for Management of MS-Related Fatigue

To date, there is limited evidence regarding the efficacy of pharmacological interventions for patients with MS. Currently, clinical practice guidelines suggest use of medications (eg, amantadine and modafinil) and rehabilitation therapies (eg, exercise, energy, or fatigue self-management).<sup>3,17</sup> However, fatigue symptoms usually respond partially to pharmacotherapy regimens that are designed to target dopaminergic norepinephrine and central-acting sympathetic adrenergic neural pathways, including amantadine and modafinil, and stimulants such as methylphenidate (Table). Fatigue also responds to medication regimens in combination with psychoeducational energy-conservation training programs.<sup>3,20</sup>

Despite advances in pharmacological and nonpharmacological treatment, MS-related fatigue continues to be the common disabling symptom in patients with MS. In current practice, both pharmacological and nonpharmacological interventions are often used in combination. Modafinil has been the most widely investigated pharmacologic intervention.<sup>10,12</sup> Research has shown that use of 200 mg of daily modafinil resulted in statistically significant reductions (ie, by 10%-25%) in fatigue scores as measured on the Epworth Sleepiness Scale, Fatigue Severity Scale, and Modified Fatigue Impact Scale.<sup>10,12,14</sup> However, a current systematic review and meta-analysis of all available studies of modafinil conducted by Rammohan et al<sup>12</sup> found no overall effect on fatigue reduction. Similar results have also been observed in nonpharmacological studies focused on evaluating the impact of aerobic exercise, behavioral-energy conservation training, and coping-skills training.<sup>3-6</sup> The benefits and barriers associated with fatigue treatment needs to be established to guide clinical care.

### IMPACT ON THE PATIENT AND CAREGIVER

Fatigue is one of the most undesirable and incapacitating of symptoms impacting individuals with MS.<sup>3</sup> Management of fatigue should include identifying and reducing any precipitating stressors, if possible, as well as educating patients to conserve their energy as best they can. Because

fatigue is an “invisible symptom,”<sup>5</sup> it may be underrecognized and undertreated by health care providers.<sup>2,10</sup> Consequently, people with MS may be perceived as just “lazy” or having a “lack of interest” in daily activities.<sup>10,17,18</sup> Symptoms such as fatigue can pose an enormous burden on the caregiver as well.<sup>17,18</sup> Thus, a holistic approach to maximizing the well-being of both patient and caregiver has become a focus of chronic disease care.<sup>18,19</sup>

Because of the complexity of symptoms, palliative care is recommended as part of the holistic approach.<sup>18</sup> Palliative care is focused on effective symptom management and decreasing distress related to the psychosocial and spiritual needs of individuals with a chronic or serious illness. The overall goal of palliative care is to provide relief from pain and other distressing symptoms and to achieve the best quality of life for patients and their families.<sup>18,19</sup> Nurses are ideally situated to assist people with MS and their families to cope with MS-related fatigue, for example, nonpharmacological interventions including education (eg, avoid heat in midday), pacing activities, and rest.<sup>10</sup>

Research is limited regarding palliative care experiences and needs of people with MS.<sup>15-19</sup> In a study using focus groups, including 16 patients with MS, participants described fatigue as “feeling wiped out” or “shut down.”<sup>15</sup> Most participants felt invalidated by those around them as if “no one gets it.”<sup>19</sup> In a second study,<sup>16</sup> patients with MS reported having difficulties expressing needs. Themes of burden and loneliness were prominent, chiefly in dysfunctional, less affluent families and among parent family members who cared for them. Almost all participants discussed the loss of support of family and friends and difficulty handling everyday life. Patients expressed the desire for more support from their families and to be viewed as distinct individuals. For example, Ghasemi et al<sup>17</sup> recommend that the palliative care concept be integrated with neurology and rehabilitative services in order to provide more comprehensive care for all MS patients.

The desire of the family member to be physically present and engaged is a constant stressor. Role confusion, emerging from each family member and the patients with MS, leads to additional problems.<sup>18,19</sup> For example, in a study with 40 dyads of patients with MS and their family members, 1 participant expressed that “he was ‘caring,’ but not a family.”<sup>18</sup> In this research, “family,” “husband/wife/partner/spouse,” “son,” “sister,” and “best friend,” are all interchanging roles. Others described themselves partially as “family” and not family members; 1 husband said he was sometimes a husband, at other times family. A number of people had come to identify fully with the role of family, some reluctantly and some with pride. Participants from this study reported that the context of family is lost when the patients with MS are bothered by fatigue.

The impact of fatigue on MS patients can be quantified by symptoms affecting the patients’ work capacity, personal





relationships and social interactions, as well as those of the family. The MS patient's inability to be employed directly impacts the spouse/family financially.<sup>20</sup> Nurses need to recognize their role of providing support to both the patients with MS as well as the family member. Similarly, the burden of fatigue on MS patients is devastating and leads to a cascade of other symptoms such as sleep disturbances, loneliness, and depression. A recent study on MS patients found that fatigue was the number 1 reason for feeling depressed, leaving the job, and reducing social activities.<sup>19,20</sup> Not only does MS affect the patient, but it also has resulted in a higher risk of depression and reduced quality of life for caregivers.<sup>3</sup> Therefore, it is important for health care providers to include interventions for the caregivers as well as the MS patient. For example, caregivers need information about available community services that could provide support for them and their loved ones. Support could include access to counseling for the caregiver. Furthermore, it is critical that caregivers receive education about respite care, which could relieve some of the stress by giving them a temporary relief.<sup>20</sup> Given the uncertainty of pharmacological interventions for fatigue, nurses and other health care providers need to concentrate on palliative care measures, such as supportive plans for the unpredictability of MS symptoms and continuity of care. The multidisciplinary team needs to be proactive and assess caregiver burden early in treatment in order to provide appropriate interventions.<sup>13</sup>

### IMPLICATIONS FOR PRACTICE

The current literature is limited on palliative care of fatigue in chronic disease, but there is a shift to support of palliative care for MS patients with regard to fatigue management. The available data emphasize the need for a holistic approach to nursing care. However, it is imperative to set the palliative care process in motion before contact with the patient is lost to follow-up.<sup>3</sup>

Health care providers need to be aware of the key symptoms that indicate fatigue at each encounter. Palliative care relieves symptoms people experience because of serious illness. These include some evidence for physical therapies as part of the palliative care regimen.<sup>6,7</sup> Health professionals need to become involved also in relapse management, disease-modifying therapies, symptom management, and palliative care, using the NMSS guidelines.<sup>13</sup>

There is widespread agreement in the literature that, because of the complex, multidimensional, and highly subjective nature of MS-related fatigue, comprehensive goal-oriented management programs that incorporate multidisciplinary expertise are required, and patients need to be evaluated regularly through appropriate clinical outcome measures. In the absence of a criterion-standard treatment for fatigue, palliative care must be the primary

focus for support. Nurses should ensure that palliative care and symptom management measures are in place for each clinic visit. Nurses and other health care providers are encouraged to use "Explore & Discuss," a resource from the NMSS<sup>10</sup> to help facilitate the conversation and help those with MS and their caregivers understand palliative care. The nurse has an important role in facilitating and coordinating these care and symptom-monitoring processes.

The case study presented provided a summary of literature and research on the study of fatigue affecting individuals with MS. We recommend that nurses work with other providers to fill the gaps in evidence-based and theoretical research related to palliative care in MS. This needs to begin with developing better ways to assess the invisible symptom of fatigue. A universally accepted measure to guide practice and capture all aspects of fatigue is needed. Rigorous qualitative and quantitative studies on pharmacologic and nonpharmacological strategies to adequately address fatigue and other symptoms are also needed.

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