

National Multiple Sclerosis Society

SLEEP DISTURBANCE AND MULTIPLE SCLEROSIS Abbey J. Hughes, PhD

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Introduction

Multiple sclerosis (MS) is a chronic disease characterized by loss of myelin (demyelination) and damage to nerve fibers (neurodegeneration) in the central nervous system (CNS). MS is associated with a diverse range of physical, cognitive, emotional, and behavioral symptoms, and can significantly interfere with daily functioning and overall quality of life. MS directly impacts the CNS by causing demyelinating lesions, or plaques, in the brain, spinal cord, and optic nerve; by contributing to overall tissue loss (atrophy) in these areas; and by interrupting communication between key neural pathways that are needed to maintain regular sensory and motor function.

Perhaps not surprisingly, damage to these key neurologic functions can disrupt basic physiological processes, including maintenance of regular sleep-wake cycles. Accumulating research has suggested that over half of individuals with MS report significant disruptions in sleep and difficulty maintaining a consistent sleep schedule. Sleep disturbance is further complicated by fatigue, which affects upwards of 90% of people with MS. The interaction between sleep and fatigue, and their combined negative impact on daily functioning has raised concern among patients and providers, and has encouraged a recent growth of research in this area.

Sleep disturbance is a general term for a wide range of sleep-related symptoms and disorders. Sleep disturbance can include:

- difficulty with initiating or maintaining sleep, also known as insomnia
- difficulty with too much sleep, also known as hypersomnia or hypersomnolence
- uncontrollable lapses into sleep, also known as narcolepsy
- sleep-related breathing difficulty, including sleep apnea
- abnormal movements during sleep, including restless legs/body syndrome
- abnormal behaviors during sleep including acting out dreams
- daytime dysfunction, including excessive daytime sleepiness

In MS, sleep disturbance is a very common, yet underdiagnosed problem, and can include any of the symptoms/conditions described above. Many individuals with MS report multiple, or co-morbid, sleep problems, such as insomnia and excessive daytime sleepiness.

In this article, we will briefly review some of the emerging research on sleep in MS, provide information on how people with MS can assess their sleep, and discuss emerging treatments for sleep disturbance in MS.

Summary of MS Sleep Research

Research over the past decade has aimed to better understand the causes of sleep disturbance in MS. Possible mechanisms by which MS can impact sleep include:

- 1. Lesions and neural damage to key brain structures involved in sleep.
 - The hypothalamus is a region of the brain responsible for many of the body's essential hormones and physiological processes (e.g., hunger/thirst, temperature regulation, stress response). Lesions or damage to this area of the brain have been shown to cause hypersomnia and narcolepsy.
 - The suprachiasmatic nucleus is a special region of the hypothalamus responsible for maintaining our 24-hour body clock. Lesions or damage to this area can make it difficult to maintain a consistent sleep-wake cycle.
 - The brain stem is essential for regulating breathing and other autonomic (involuntary) nervous system functions during sleep, including maintaining paralysis during sleep so that we do not act out our dreams. Lesions or damage to this area can result in disrupted breathing during sleep (sleep apnea) and sleep behavior disorders.
- 2. Disruption of key neurotransmitters involved in sleep.
 - The neuropeptide hypocretin, or orexin, is an important molecule produced by the hypothalamus that helps to regulate arousal. Abnormally low levels of hypocretin can result in narcolepsy.
 - The neurotransmitters dopamine and norepinephrine play an important role in movement, cognition and motivation. Disruptions in key dopamine and norepinephrine pathways may explain some of the fatigue experienced by people with MS.
 - The neurohormone melatonin plays an important role in regulating sleep-wake cycles. Lower levels of melatonin have been associated with poorer sleep efficiency and seasonal MS relapses.
- 3. Deficiencies in Vitamin D and other nutrients that may help regulate sleep. Vitamin D deficiency has been linked to sleep disorders. Given that people with MS are more prone to vitamin D deficiency than the general population, additional research is being conducted to assess the relationship between vitamin D and sleep in MS.

- 4. Secondary effects of common MS symptoms.
 - In addition to the direct effects of MS on sleep, MS can also cause a number of symptoms that indirectly disrupt sleep.
 - Restless Legs/Limbs/Body: people with MS often report wakening in the middle of the night due to muscle cramps, muscle spasms, and restless legs/limbs/body.
 - Pain: Pain is reported in one-third to one-half of people with MS. Awakening due to pain (e.g., neuropathic pain, cramping and headache pain) can significantly disrupt sleep.
 - Urinary/bowel symptoms: Urinary and bowel frequency and incontinence are commonly reported among people with MS. Nocturia (nighttime urinary symptoms) are especially common and can disrupt sleep.
 - Temperature dysregulation: People with MS often report becoming easily overheated. Awakening due to overheating, sweating and temperature discomfort also disrupt sleep.

5. Side effects of MS medications.

- Disease-modifying therapies (DMTs): In general, sleep disturbance is not commonly associated with use of DMTs. However, insomnia has been reported as a potential side effect of alemtuzumab.
- Corticosteroids for MS relapse/exacerbation: Intravenous and oral
 corticosteroids are often given for a period of 3-7 days during an MS
 relapse/exacerbation. Insomnia and excessive daytime sleepiness are common
 side effects of steroid treatment. Fortunately, these side effects are temporary
 and resolve after completion of steroid treatment.
- Stimulant medications for fatigue: Stimulant medications such as modafinil, amantadine and methylphenidate are often prescribed to help treat MS-related fatigue. Stimulants can cause restlessness and disrupt sleep. Fortunately, adjusting the dosage and timing of administration can mitigate these side effects.
- 6. Increased napping during the day due to fatigue.

 To cope with fatigue, people with MS often feel the need to nap throughout the day.

 Unfortunately, naps that are too long in duration (> 1 hour), or naps that are taken too close to bedtime (within 5-6 hours) can make it more difficult to fall asleep.
- 7. Reduced physical activity due to fatigue and MS-related disability.

 Maintaining regular physical activity is important for regulating sleep. Fatigue and physical disability often lead to decreased physical activity in MS. People with MS may give up daily cardiovascular activity (e.g., running, walking), or feel less motivated to do physical activity.

8. Effects of stress and anxiety.

Stress and anxiety are among the most common causes of insomnia in MS. People with MS report frequent worry about their disease and uncertainty about the future. Ruminating about these issues prior to sleep can make it more difficult to fall asleep and to obtain restful sleep. People who are stressed and anxious also tend to have more periods of wakefulness during the night, making their sleep time less efficient (defined by the ratio of time in bed asleep in relation to their time in bed awake).

9. Effects of depression.

One of the key symptoms of depression is sleep disturbance. Depression is common in MS, affecting approximately 50% of patients. Depression can cause insomnia as well as hypersomnia.

10. Changes in sleep hygiene behaviors (e.g., not having a regular sleep/wake time). Sleep hygiene refers to behaviors that promote sleep quantity and quality. Examples of poor sleep hygiene include: doing non-sleep activities (e.g., watching TV), using tobacco products, drinking caffeine and/or alcohol, watching the clock, or engaging in overstimulating activities right before bed.

In a 2011 study, 473 people with MS were surveyed to identify variables most commonly associated with sleep disturbance. Results showed that depression, spasticity/leg cramps, pain, fatigue and nighttime urinary urgency/frequency were all significantly associated with worse sleep. Older female patients with longer disease duration tended to have poorer sleep. Additionally, although approximately 30% of patients reported taking some form of sleep medication (prescription and/or over-the-counter), patients taking those medications continued to report poor sleep.

Another series of studies used polysomnography (PSG), the gold-standard method for assessing sleep disturbance, to assess the severity of sleep problems in MS and their impact on quality of life. Results showed that compared to people without MS, people with MS spent more time awake throughout the night, had less efficient sleep, had a greater number of awakenings, and spent less time in the important restorative stage of sleep (REM sleep). Additionally, poor sleep had a significant impact on mental health status. Taken together, these studies highlight the prevalence of sleep disturbance and the negative impact of sleep disturbance on health-related quality of life in MS.

Emerging Treatments for Sleep Disturbance in MS

Treating sleep disturbance in MS can be quite challenging due to its many potential causes, as well as potential side effects of some treatments. Here, we review the most common treatments available, potential side effects, and tips for improving your sleep. Importantly, sleep is an important part of maintaining a balanced, healthy lifestyle. Many of these tips can be beneficial to people without sleep disorders. Caregivers for people with MS may also benefit from some of these tips.

1. Medications

- Sedative medications such as benzodiazepines (e.g., alprazolam, clonazepam, diazepam), non-benzodiazepine hypnotics (e.g., zopidem, eszopiclone), and antihistamines (e.g., dimenhydrinate, diphenhydramine) are commonly prescribed to people with MS for short-term treatment of insomnia. Unfortunately, these medications often fail to effectively treat insomnia, are associated with a number of physical and cognitive side effects, and are not indicated for long-term use.
- Symptom management medications are medications that aim to treat a
 particular MS symptom that is believed to be causing sleep disturbance (e.g.,
 urinary/bowel symptoms, restless legs/limbs/body). Depending on your
 symptoms, a neurologist, physiatrist, or urologist who specializes in MS may
 help identify which symptom management medications may be a fit for your
 treatment needs.

2. Medical Equipment

- Continuous positive airway pressure (CPAP) is the most effective treatment for sleep apnea. CPAP machines usually consist of a nosepiece or face mask connected to an air pump that delivers consistent oxygen flow to keep your airway open during sleep. Improvements in CPAP machinery over the past decade have been substantial and these devices are now made to be more lightweight, quiet, and easy-to-use.
- Bright light therapy lamp/boxes are highly effective for treating depression and seasonal affective disorder. For individuals whose sleep-wake cycles have become disrupted, daily use of a full-spectrum, 10,000-lux bright light therapy lamp can be effective. Consult your doctor before beginning a bright light therapy regimen because it should not be used with certain medical conditions (e.g., retinal or ocular disease, bipolar disorder).

- 3. Behavioral Medicine: Cognitive Behavioral Therapy (CBT) and Cognitive Behavioral Therapy for Insomnia (CBT-I)
 - Cognitive Behavioral Therapy (CBT) is among the most effective treatments for depression, anxiety, insomnia, and a number of other mental health and behavioral conditions. CBT focuses on identifying and changing unhelpful patterns of thinking and behavior, and replacing those thoughts and behaviors with more adaptive strategies. CBT has been extensively studied and has been shown to be effective for reducing depression and improving symptom management in MS.
 - CBT for Insomnia (CBT-I) is a type of CBT that specifically focuses on identifying and changing unhelpful thoughts and behaviors that interfere with sleep. Key components of CBT-I include:
 - o Keeping a weekly sleep diary to track sleep quantity and quality
 - o Using the bed only for sleep and intimacy, also called stimulus control
 - Sleep efficiency training, also called sleep restriction therapy (to improve the ratio between time spent asleep in bed in relation to time spent awake in bed)
 - o Engaging in behaviors that promote sleep, also called sleep hygiene
 - o Monitoring and challenging unhelpful thoughts/beliefs about sleep
 - Using relaxation/meditation/mindfulness strategies
 - CBT and CBT-I are short-term treatments, typically delivered in 4-12 weekly sessions. CBT and CBT-I have equivalent short-term efficacy to medications, but often support better long-term outcomes without negative side effects.
 - For more information on CBT-I, visit https://sleepfoundation.org/sleep-news/cognitive-behavioral-therapy-insomnia/.

Tips for Assessing Your Sleep

Assessing your sleep is the first step to identifying sleep-related problems and/or clinically significant sleep disorders. Before your next medical appointment, it may be helpful to ask yourself the following questions, and bring your responses with you to your health care provider.

Durii	ng the past month:
1.	How long, on average, has it taken you to fall asleep?
2.	How many hours of sleep, on average, did you get per night?
3.	How many times, on average, did you wake up per night?
4.	How many minutes per night, on average, did you spend in bed awake, unable to fall back asleep?
5.	How rested, on average, did you feel upon waking in the morning?Not rested at allA little restedModerately restedFully rested
6.	How often, on average, did you take naps during the day?Not at allSome daysMost daysEvery day
7.	How often did pain interfere with your sleep? Not at allSome daysMost daysEvery day
8.	How often did spasticity/restless legs/limbs/body interfere with your sleep?Not at allSome daysMost daysEvery day
9.	How often did urinary/bowel symptoms interfere with your sleep?Not at allSome daysMost daysEvery day
10.	How often did you take medication (prescription or over-the-counter) to help with sleep? Not at allSome daysMost daysEvery day
11.	How often did you snore or experience shortness of breath upon waking?Not at allSome daysMost daysEvery day
12.	How difficult was it to maintain alertness and energy during the day?Not difficultSomewhat difficultModerately difficultVery difficult

After discussing these questions with your health care provider, you may be asked to participate in a formal sleep study. A sleep study is an overnight observation of your sleep behaviors that often involves polysomnography (PSG). PSG involves wearing lightweight wires to monitor your brain activity, heart rate, blood pressure and other physiological processes. PSG studies can be done at your doctor's office, or in some cases, in your own home. Your doctor can help decide what type of sleep study would be the best match for your symptoms. After your sleep study, you will discuss your results and available treatments with your doctor.

Additional Tools and Resources

The following links provide additional tools and strategies for learning about the causes, assessment, and treatment of sleep disturbance in MS:

- University of Washington MS Rehabilitation Research and Treatment Center Sleep and MS Factsheet: http://msrrtc.washington.edu/info/factsheets/sleep
- National MS Society website, further resources regarding sleep:
 - o Get the Sleep You Need!: <u>nationalmssociety.org/getsleep</u>
 - o Managing Pain and Sleep in MS: <u>nationalmssociety.org/sleep</u>
- US Department of Veterans Affairs CBT-I Coach (smartphone app): https://mobile.va.gov/app/cbt-i-coach
- National Sleep Foundation website: https://sleepfoundation.org/sleep-disorders-problems/ms-and-sleep
- Veterans Affairs MS Centers of excellence website:
 va.gov/MS/articles/Easy and Common Tips for Good Sleep.asp
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