

# Sleep Disorders in Patients With Multiple Sclerosis

Identifying and treating sleep problems can help optimize the well-being and function of patients with multiple sclerosis.

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Despite our understanding that sleep disorders are more prevalent in and have significant impact on persons with multiple sclerosis (MS), sleep disorders often remain unaddressed in routine clinical evaluation of patients with MS. Some of the most commonly encountered, consequential, and yet treatable sleep disorders in patients with MS include chronic insomnia, sleep-disordered breathing (SDB), and restless legs syndrome (RLS). Enhanced understanding of potential causes, consequences, and presentations of common sleep problems may offer new opportunities to optimize function and quality of life for patients with MS.

## Consequences of Poor Sleep

Along with traditional measures of disability, there are invisible symptoms of MS that carry substantial morbidity, including fatigue, pain, mood disturbances, and cognitive dysfunction. An important component of clinical management for patients with MS includes identifying treatable or reversible comorbid conditions that can contribute to and worsen these symptoms.

## Fatigue

Sleep problems contribute significantly to the fatigue that affects up to 90% of persons with MS at some point during their disease course, which is a leading cause of decreased quality of life with significant socioeconomic consequences.<sup>1,2</sup> (See *Fatigue in Patients With Multiple Sclerosis* p. 43) Although the primary mechanism(s) underlying MS-related fatigue have yet to be fully elucidated, several treatable comorbidities—including sleep disorders and disturbances—are recognized as important secondary causes of fatigue in MS. Recent studies suggest that insomnia, obstructive sleep apnea (OSA), and RLS in particular are independent predictors of fatigue in patients with MS,<sup>3-5</sup> and that successful treatment of these conditions may improve fatigue.<sup>6,7</sup>

## Mental Health and Cognition

Sleep disturbances are also associated with mood disorders among persons with MS.<sup>8</sup> Bidirectional relationships between sleep disturbances, pain, and depression are common,<sup>9</sup> and sleep disturbances may be key mediators of relationships between pain and depression.<sup>10</sup>

Cognitive dysfunction is experienced by at least 50% of persons with MS, constituting a major cause of loss of employment and reduced quality of life.<sup>11</sup> Impairment in verbal and visual memory, executive function, processing speed, and calculation are common, even in patients who seem otherwise relatively unaffected by the condition. Interestingly, an emerging body of evidence has linked sleep disturbances to cognitive dysfunction in MS, although measures of sleep and cognition across studies have been variable. A 2016 cross-sectional study using polysomnography and the Minimal Assessment of Cognitive Function in MS (MACFIMS), a validated, 90-minute battery composed of 7 standard cognitive tests, demonstrated significant associations between OSA and objective measures of working memory, processing speed, attention, verbal learning, and response inhibition, adjusting for depressive symptoms.<sup>12</sup> Other studies, however, focused on subjective sleep and self-reported cognitive dysfunction, suggest that depression and fatigue may mediate this relationship.<sup>13,14</sup> Additional studies that incorporate potential mediators (eg, fatigue and depression) and utilize standardized measures of sleep and cognition are needed to fully elucidate the causal pathway between sleep and cognition in patients with MS. This work highlights a potentially new opportunity to treat cognitive impairment in MS.

## Common Sleep Disorders

### Chronic Insomnia

Insomnia is characterized by difficulty initiating or maintaining sleep and can exist as a symptom, or as a disorder, in which case symptoms of insomnia are associated with some

form of distress about poor sleep, or lead to impairments in social, academic, or vocational functioning. Pertinent criteria for chronic insomnia disorder from the International Classification of Sleep Disorders Diagnostic Manual, Third Edition are in Box 1.<sup>15</sup>

Within this framework, up to 40% of patients with MS may be at risk for insomnia.<sup>4,5</sup> Some of the most common MS symptoms including chronic pain, neurogenic bladder, spasticity, and comorbid anxiety and depression all have the potential to interfere with sleep initiation, sleep maintenance, or sleep perception.<sup>4</sup> Concomitant sleep disorders and use of daytime wake-promoting agents or stimulants for fatigue can also contribute to insomnia symptoms in patients with MS.

### Sleep-Disordered Breathing

SDB includes central sleep apnea (CSA) and OSA, the latter of which is characterized by repeated episodes of upper airway obstruction and hypoxia during sleep. Although larger population-based studies are still needed, current research suggests a higher prevalence of OSA in patients with MS compared to the general population. The reason for this association is still unknown. Although patients with MS may have many of the same risk factors, they may also have other neuroanatomical risk factors contributing to SDB. For example, brain stem sensory and motor network impairments could affect airway patency and respiratory drive. Progressive MS subtypes and increased disability levels have been linked to SDB in persons with MS. There is a link between brainstem lesion burden and both obstructive and central sleep apnea in patients with MS, and progressive MS is associated with increased apnea severity, controlling for age and body mass index.<sup>16</sup>

Although prevalence of SDB in persons with MS seems higher than in the general population, OSA appears under-recognized. Although >50% of patients with MS seen in a tertiary care center may be at elevated risk for OSA (based on a common OSA screening questionnaire), only 20% of these patients carried an OSA diagnosis,<sup>4</sup> suggesting a high frequency of underevaluation. A similarly designed community-based study of patients who self-identified as having MS showed that although up to 21% were at risk for OSA based on the STOP-BANG criteria, only 4% had received an OSA diagnosis.<sup>5</sup> Collectively, these studies highlight a significant disparity between OSA risk and recognition among patients with MS.

Repeated complete or partial airflow reduction, due to intermittent lack of respiratory effort defines CSA. Although the exact prevalence of CSA in persons with MS is unknown, several studies suggest that particularly those with brainstem involvement or who are more disabled have an elevated risk for CSA.

### Restless Legs Syndrome

Defined as a restlessness or uncomfortable sensation of the

## ▶▶▶ Box 1. International Classification of Sleep Disorders-3 Insomnia Definition

- ❑ Despite opportunity and circumstances for sleep, persistent difficulty with
  - ❑ sleep initiation
  - ❑ sleep duration
  - ❑ sleep consolidation
- ❑ Resulting in 1 or more daytime impairments, including
  - ❑ fatigue
  - ❑ impaired concentration or memory
  - ❑ mood disturbances
  - ❑ excessive daytime sleepiness
  - ❑ behavioral problems
  - ❑ reduced motivation or energy
  - ❑ impaired social, family, academic, or occupational performance
  - ❑ proneness to errors
  - ❑ concerns or dissatisfaction with sleep
- ❑ Subtypes include
  - ❑ insomnia due to a medical condition
  - ❑ insomnia due to another mental disorder

lower extremities that is exacerbated by rest, RLS occurs in the evening or before bedtime, and is relieved by movement.<sup>17</sup> Patients use many descriptors to describe the restless sensation, including creeping, crawling, itching, burning, tightening, or tingling. Others describe this sensation as painful.

The disorder is classified as idiopathic or primary if no other cause can be identified, or secondary if caused by another comorbid condition known to increase vulnerability (eg, MS) (Box 2).<sup>15,17</sup>

The majority of studies suggest that RLS is 3 times more prevalent in patients with MS than in the general population.<sup>18,19</sup> Although reasons for increased prevalence are speculative, there is a proposed role for dysfunction of downstream dopaminergic pathways<sup>20</sup> that project to the spinal cord, are responsible for the suppression of sensory inputs and motor excitability and are susceptible to damage from diseases that affect the spinal cord. This hypothesis may explain the increased prevalence of secondary RLS in patients with MS and is supported clinically by research

## ▶▶▶ Box 2. International Classification of Sleep Disorders-3 Restless Leg Syndrome Definition

Diagnosis of restless leg syndrome requires 4 criteria

- restlessness or uncomfortable sensation of the lower extremities
- exacerbated by rest and inactivity
- tendency to occur in the evening or before bedtime
- relieved with movement

AND

- not better accounted for by another medical or behavioral condition

AND

- causes concern, distress, sleep disturbance, or daytime impairment

demonstrating associations between RLS and spinal cord pathology.<sup>21</sup> Certain medications used in the management of persons with neurologic conditions, such as antiemetics, antipsychotic dopamine antagonists, antidepressants, and antihistamines can also cause or worsen RLS.

Several other symptoms that may be particularly common in MS, such as cramping, clonus, spasticity, or in particular, neuropathic pain<sup>22</sup> can be difficult to discern from RLS and often require detailed, direct questioning (see next section).

### Diagnosis and Management of Sleep Disorders Insomnia

**Diagnosis.** All patients with MS who endorse symptoms of daytime impairment (which strongly overlap with chronic MS symptoms) or express concerns about prolonged sleep latency, fragmented sleep, unrefreshing sleep, or early terminal awakenings should be evaluated for insomnia. Given the strong association between sleep disturbances, pain and depression, and the contributions of spasticity and neurogenic bladder disorders to sleep disturbances, patients who endorse any of these symptoms should also be evaluated for sleep disorders. As with any patient, external factors or habits that may interfere with sleep hygiene should also be assessed. Formal sleep testing is not routinely indicated to confirm a diagnosis of insomnia unless there is suspicion of a concomitant sleep disorder (eg, OSA or periodic limb movement disorder) that may contribute to insomnia.

**Management.** Appropriate sleep hygiene and amelioration of any precipitating causes is a first cardinal step.

Minimize medications or substances that may contribute to insomnia, if possible, and for patients who require stimulants to address daytime fatigue, consider alternative (earlier) dosing schedules. Anticonvulsants and antispasmodics, used to treat neuropathic pain and spasticity respectively, have sedating properties and may be useful for nocturnal symptoms. Because depression has a bidirectional relationship with insomnia, if present, both conditions should be treated in tandem.

If insomnia symptoms are not amenable to treatment of secondary causes, or no secondary cause is identified, referral to a sleep specialist is suggested (see next section). In this case, behavioral strategies are favored over pharmacologic options. If hypnotics are necessary, benzodiazepines, benzodiazepine agonists, and melatonin-receptor agonists are the most extensively studied for chronic insomnia. Orexin receptor antagonists, while generally well-tolerated, may be associated with sedation, vivid dreams, worsening depression, and complex nighttime behaviors. Avoid anti-histamine-containing products in patients with MS because they may cause psychomotor impairment; recent evidence suggests antihistamines are independently associated with increased daytime fatigue in patients with MS.<sup>23</sup>

### Sleep-Disordered Breathing

**Diagnosis.** Because of the potential consequences and high prevalence of SDB in patients with MS, screening for signs and symptoms associated with sleep apnea is recommended and includes assessment of snoring, gasping or choking upon awakening, nonrestorative sleep, nighttime arousals, fatigue, and excessive daytime sleepiness. Signs of brainstem dysfunction (eg, dysarthria or dysphagia brainstem lesions on MRI could signal a high risk of SDB and warrant sleep apnea evaluation with polysomnography (PSG). In-laboratory sleep studies are preferable to home sleep studies because of the prevalence of CSA and other sleep disorders in patients with MS that are not as sensitively detected remotely.

**Treatment.** Sleep apnea treatments for patients with MS are similar to those for patients without MS. Positive airway pressure (PAP) therapy is the preferred treatment modality. If PAP therapy is selected, existing neurological deficits and symptoms should be taken into consideration when selecting a mask interface. For example, patients with significant dexterity issues or hemiparesis may do best with masks that do not have complex setups. Patients with a history of trigeminal neuralgia may benefit from masks that minimize facial contact.

Alternatives to PAP therapy have not been sufficiently studied in patients with MS; however, assuming permanent resolution of apnea is the goal of surgery, the underlying anticipation of changing neurological function usually makes surgery less attractive. Careful consideration of postsurgical risks is also necessary and should involve consultation with

an MS specialist, especially if patients are on concomitant immunosuppressive therapies. Although there are generally no MS-specific contraindications to oral appliances if otherwise clinically indicated, additional studies are necessary to determine their clinical utility and feasibility in patients with MS. These devices may also be inappropriate for patients with trigeminal neuralgia who experience pain triggered by oral stimulation.

For the treatment of CSA, options should be selected based on underlying pathophysiology and tailored to the primary cause of CSA, in coordination with a sleep specialist (next section). Treatment may include supplemental oxygen, bilevel PAP, or adaptive servoventilation. Because use of CNS-depressing medications such as opiates or antispasmodics may also worsen CSA, these agents should be minimized whenever possible.

### Restless Legs Syndrome

**Diagnosis.** A useful, efficient screen question can be used in a busy clinical setting: “When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?”<sup>24</sup> A positive response warrants subsequent detailed questioning to determine if diagnostic criteria (Box 2) are present. Diagnosis of RLS should not require PSG unless there is concern for an alternative or contributing sleep disorder. However, even with detailed questioning, distinguishing between RLS and other symptoms can be challenging. For example, neuropathic pain may be more prominent or noticeable at night suggesting a circadian predilection. In this case, endorsement of relief with movement, even if the relief is only temporary while the movement continues, supports diagnosis of RLS. Persistent pain that is not ameliorated by movement suggests neuropathic pain. Spasticity or clonus may be more noticeable at night, and during times of fatigue later in the day. In this case, asking about the nature of the leg movements may be useful. Sensations of leg tightness relieved by voluntary movement suggest RLS, whereas involuntary spasms suggest spasticity even if a circadian component is present. Rhythmic involuntary movements triggered by stretch or certain leg positions suggest clonus.

**Treatment.** Although no MS-specific comparative efficacy studies for management of RLS are available, in the author’s experience, treatment should be individually tailored based on symptom frequency and severity and the presence of any other comorbidities. As patients may have concomitant risk factors for idiopathic RLS, which is often associated with iron deficiency, iron studies are recommended. If ferritin levels are <50 ng/mL, initiate iron supplementation. Reduction or discontinuation of medications and substances that can cause or worsen RLS (see previous section) is also advised.

If the above strategies are ineffective, or no RLS triggers are identified, dopamine agonists or  $\alpha$ -2- $\delta$  ligands may be

indicated. Because dopaminergic agents may be associated with nausea, hypotension, hallucinations, and dyskinesias, use caution with these agents when treating patients with advanced MS who may have concomitant autonomic dysfunction. Dopaminergic agents are also associated with augmentation, which is a phenomenon that involves worsening of RLS symptoms earlier in the day, with geographic spread to other body regions. In contrast, these concerns are not present when treating with  $\alpha$ -2- $\delta$ -ligands, making them attractive options for treatment of RLS in patients with MS. Anticonvulsants, including gabapentin, carbamazepine, and pregabalin are effective treatments and may be ideal for patients who suffer from concomitant conditions such as neuropathic pain or seizures, or for patients who have experienced significant issues with augmentation on dopaminergic agents.

### Referral to a Sleep Specialist

Given the value of a multidisciplinary MS care model, sleep specialists have the potential to provide useful contributions to the management of patients with MS. Although the primary provider for a patient with MS may choose to work up and manage straightforward sleep problems, there are several situations in which consultation with a sleep medicine specialist is recommended. Patients with suspected parasomnias or narcolepsy (not discussed in this article) are usually referred for diagnosis and management by sleep specialists. Patients with chronic insomnia who could benefit from behavioral strategies should consult with sleep specialists to determine if they may be candidates for cognitive behavioral therapy for insomnia, or CBT-I, which aims to target maladaptive thoughts and behaviors that can perpetuate insomnia. The benefits of CBT-I are well studied in the general population, and recent research anticipates a similar benefit for patients with MS.<sup>25</sup> Patients with CSA, those with OSA who are having difficulty tolerating PAP, or those who do not respond optimally to PAP, may also benefit from referral to a sleep clinic. Finally, patients with RLS who do not respond to typical first-line or second-line therapies, or experience augmentation in response to dopaminergic therapy, could also benefit from sleep specialty care.

### Conclusion

Chronic insomnia, SDB, and RLS are common but frequently underrecognized conditions in patients with MS. Neuroanatomical features, concomitant comorbidities, and medications associated with MS may partially explain the high prevalence of these disorders in this population. Given recent associations between sleep disorders and some of the most disabling chronic symptoms of MS, dedicated efforts to identify and treat sleep disorders may provide new avenues to optimize the health and well-being of persons with MS. ■

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