

# Sleep Disorders in Neuromuscular Diseases

Eric J Gartman

The Warren Alpert School of Medicine of Brown University Division of Pulmonary, Critical Care, and Sleep Medicine, Providence VA Medical Center, Providence, RI, US

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Disturbances in sleep are common in patients with neuromuscular diseases (NMDs) and are the source of a significant amount of morbidity. Underlying these disorders of sleep are the physiologic alterations that result from progressive changes in muscle strength, effective ventilation, and control of respiration. This review will discuss the normal changes that occur during sleep, how the physiologic alterations present in neuromuscular and chest wall disorders affect these normal processes, how to assess patients for the presence of sleep disorders, and how to approach treatment.

## Keywords

Sleep disorders; neuromuscular diseases; respiratory physiology; treatment

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**Corresponding Author:** Eric J Gartman, The Warren Alpert School of Medicine of Brown University Division of Pulmonary, Critical Care, and Sleep Medicine, Providence VA Medical Center, Providence, RI 02908 US. E: [eric\\_gartman@brown.edu](mailto:eric_gartman@brown.edu)

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## Highlights

- Neuromuscular diseases exhibit a complex array of respiratory physiologic changes that typically progress over time.
- These physiologic changes can promote significant respiratory abnormalities during sleep, leading to decreased quality of life, significant daytime symptoms, and overall worse survival.
- There should be a high index of suspicion for the emergence of sleep-related disorders, especially since ventilatory issues during sleep can precede awake ones.
- Patients should undergo a thorough clinical and laboratory evaluation and early referral for sleep evaluation with overnight polysomnography should be considered.
- Non-invasive ventilation is the mainstay treatment for sleep-disordered breathing and hypoventilation in these patients and has been shown to promote a wide range of positive outcomes.

Disturbances in sleep are common in patients with neuromuscular diseases (NMDs) and are the source of a significant amount of morbidity.<sup>1-4</sup> Underlying these disorders of sleep are the physiologic alterations that result from progressive changes in muscle strength, effective ventilation, and control of respiration. This review will discuss the normal changes that occur during sleep, how the physiologic alterations present in neuromuscular and chest wall disorders affect these normal processes, how to assess patients for the presence of sleep disorders, and how to approach treatment.

## Normal physiology during sleep

The sleep state demonstrates predictable effects on the respiratory system and control of ventilation, which generally have little physiologic consequence. Normal sleep progresses and cycles through three phases of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep – with most adults spending approximately 25% of sleep in REM.<sup>5</sup> The patterns of breathing, ventilation, and muscle tone vary between REM and NREM sleep. At the initiation of sleep (NREM), ventilation declines due to a regular and more shallow breathing pattern.<sup>6</sup> There is a reduction in upper airway muscle tone and a resultant increase in airway resistance.<sup>7</sup> These, in combination with a reduced chemosensitivity and wakefulness drive to breathe, lead to a mild predictable rise in the partial pressure of carbon dioxide (pCO<sub>2</sub>).<sup>8-11</sup>

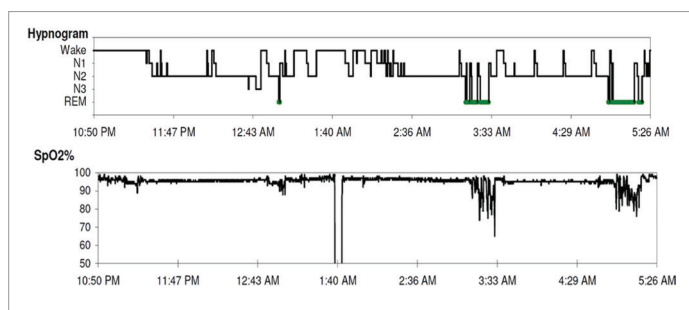
With progression into REM sleep, the pattern of breathing becomes irregular with variations in respiratory rate and tidal volume.<sup>12,13</sup> Chemosensitivity to low partial pressures of oxygen (pO<sub>2</sub>) and elevations in pCO<sub>2</sub> declines further.<sup>10,14,15</sup> Skeletal muscle tone is significantly reduced, with the exception of the eye and diaphragm muscles—and thus contributions from other muscles of respiration

**Table 1: Physiologic changes promoting sleep disturbances in neuromuscular and chest wall disorders**

1. Pulmonary restriction (chest wall stiffness, positional decline in lung volume, inspiratory muscle weakness)
2. Increase in upper airway resistance
3. Hypoventilation (especially during REM atonia)
4. Decline in chemosensitivity to blood gas changes (hypercapnia, hypoxemia)
5. Central nervous system-related events and secondary periodic breathing (e.g. Cheyne-Stokes)

REM = rapid eye movement

**Figure 1: Hypnogram of patient with significant diaphragmatic weakness**



During the transition to REM from non-REM, there are profound hypoxemic events. Concurrent airflow and effort tracings did not suggest apneas/hypopneas as the etiology of hypoxemia (i.e., suggests hypoventilation). Sleep stages labeled on y-axis, and REM periods highlighted. REM = rapid eye movement.

are minimal.<sup>16–18</sup> Due to this muscle atonia, upper airway resistance rises further in REM sleep.<sup>19–21</sup>

In general, lung volumes (specifically functional residual capacity) are reduced in the supine position and during sleep and can be accentuated during periods of muscle atonia.<sup>22–24</sup>

### Effects of sleep in neuromuscular disease

Patients with neuromuscular and restrictive chest wall diseases can commonly be affected by sleep disorders resulting from a combination of airway muscle weakness, chest wall/rib cage stiffness, and diaphragmatic and respiratory muscle weakness.<sup>25</sup> The pattern of respiratory system involvement in a given condition determines the risk for a given type of sleep-disordered breathing.<sup>26</sup> Further, unfortunately, many of these disorders have marked progression over time and their effects on sleep become more pronounced. A summary of the common physiologic changes discussed below is displayed in *Table 1*.

### Hypoventilation during sleep

As patients with NMD progress, issues with hypoventilation ensue. Importantly, given the sleep physiology discussed above, hypoventilation during sleep will precede awake hypoventilation (so one should not wait for evidence of daytime hypoventilation to consider evaluating a given patient’s sleep). Initially, given the normal muscle atonia during REM and the burden of ventilation solely placed on the diaphragm muscles, sleep hypoventilation first presents during this sleep stage (*Figure 1*).<sup>1,27–29</sup> This effect can be amplified in children with NMDs, since they spend a longer

time in REM sleep.<sup>30</sup> With worsening of muscle weakness over time, hypoventilation eventually occurs during NREM sleep as well.<sup>1,31</sup>

### Respiratory muscle weakness

The underlying driver of hypoventilation during sleep is weakness of the respiratory muscles, most importantly, the diaphragm muscles. Further, when diaphragm weakness and/or paralysis is present, the effect of body position during sleep can be substantial—as has been shown in disorders of isolated unilateral and bilateral paralysis where the vital capacity can decline 15–40%, respectively, by assuming a supine posture.<sup>32–34</sup>

Diaphragm weakness or paralysis is a common feature of many NMDs. In patients with amyotrophic lateral sclerosis (ALS), phrenic nerve involvement and associated diaphragm weakness has been shown to lead to hypoventilation and nocturnal hypercapnia.<sup>28,35–37</sup> In patients with Duchenne muscular dystrophy, hypoventilation during sleep has been demonstrated and is likely related to the degree of diaphragm involvement; although, predicting sleep hypoventilation based on pulmonary function values has been shown to be somewhat unreliable, except possibly in patients with significantly reduced expiratory flows.<sup>38–41</sup> Diaphragmatic insufficiency is common in acid maltase deficiency (Pompe’s disease) and significant hypoventilation and oxygenation deficiencies have been demonstrated, especially during REM sleep.<sup>31,42</sup>

### Chest wall disorders

Ventilatory abnormalities during sleep can arise in patients with abnormal chest walls, such as patients with congenital deformities and acquired musculoskeletal disorders. Alterations in the thoracic cage can lead to deleterious effects on chest wall mechanics and respiratory efficiency, as well as reductions in overall lung volume. Taken together, these issues predispose such patients to impaired inspiratory muscle function and subsequent sleep hypoventilation and hypoxemia.<sup>43,44</sup>

### Upper airway musculature/resistance

Resistance in the upper airway normally increases during sleep,<sup>31,45</sup> and certain anatomic factors may make one susceptible to the development of sleep apnea (and these factors obviously remain important in patients with NMD).<sup>20</sup> In patients with NMD, the progressive physiologic changes that occur in some disorders further predispose them to significant issues with sleep-disordered breathing/sleep apnea. Given the concurrent inspiratory (diaphragmatic) weakness that can be present, it can be difficult to decipher obstructive apneic/hypopneic events from hypoventilatory/diaphragmatic events.<sup>46</sup>

In patients with NMDs affecting the bulbar muscles, it has been demonstrated that they can have abnormalities suggesting upper airway collapse and flow truncation and oscillation during pulmonary function testing and on flow-volume loops; additionally, it was shown that those with the most abnormal testing went on to develop frank respiratory failure in the future.<sup>47–49</sup> The magnitude of effect on sleep-disordered breathing in patients with significant bulbar involvement is unclear, but it intuitively follows that patients with this pattern of weakness may have more profound airway issues during sleep. For example, obstructive events were found to be more prevalent in ALS patients with bulbar involvement than without.<sup>50</sup> However, other studies have suggested that sleep disruption and blood gas abnormalities may be more attributable to weakness and hypoventilation, as opposed to true obstructive sleep events.<sup>28,51</sup>

Similarly, in studies in patients with post-polio syndrome, bulbar involvement was shown to either lead to mostly central sleep events or to not increase the frequency of sleep-disordered breathing compared to those without bulbar involvement.<sup>52,53</sup>

Several types of NMDs have been reported to exhibit a potential bimodal pattern of appearance over time, meaning that one sleep-disordered breathing pattern predominates in the earlier stages of the disease (or at younger ages) and then another is evident in the latter part. Patients with Pompe's disease (acid maltase deficiency) have been shown to have obstructive events due to body habitus early in their course, followed by a predominance of hypoventilation and pseudo-central events later.<sup>31,42,45</sup> In a similar fashion, patients with Duchenne muscular dystrophy have demonstrated primarily obstructive sleep apnea events early in life, followed by the development of sleep hypoventilation.<sup>39,54,55</sup> Notably, these studies showed that a combination of both obstructive events and hypoventilation can be present to some degree, especially in the transition period between early and latter stages of disease. Further, as mentioned above, misclassification of events as obstructive versus pseudo-central or hypoventilatory in a given study may lead to erroneous conclusions.<sup>56</sup>

Sleep-disordered breathing patterns in patients with spinal cord injury can vary by the level of injury and can be a combination of obstructive and central/hypoventilation events. In patients with cervical spine injuries, sleep apnea can be a common finding, with additional hypoventilatory issues being present the more the diaphragm is involved.<sup>57,58</sup> It has been suggested that spinal cord injury patients are at increased risk of obstructive sleep apnea due to an increase in collapsibility of the upper airway.<sup>59–61</sup> Further, patients with spinal cord injury can develop an increase in neck circumference, which predisposes them further to sleep-disordered breathing (in this case, mainly obstructive events).<sup>57,62</sup>

Finally, there have been several reports of a potential increased risk of obstructive sleep apnea events in Charcot-Marie-Tooth disease. One report of this association was from a family with the condition, and it was postulated that the mechanism of sleep-disordered breathing was pharyngeal neuropathy.<sup>63</sup> An additional study reported a relatively high rate of sleep apnea in these patients compared with controls.<sup>64</sup>

### Central involvement

In addition to sleep disturbances resulting from respiratory muscle weakness, physiologic changes in the chest wall, and upper airway resistance changes, patients with NMDs can have sleep abnormalities associated with central events and control of breathing. Prominent and progressive hypoventilation in many of these disorders leads to blunted responses to hypercapnia and hypoxemia, which in turn, may lead to compensatory mechanisms (e.g. retention of bicarbonate by the kidney) that may further decrease responsiveness to abnormal blood gases and progressively worsen overall ventilation.<sup>65,66</sup>

Several unique centrally-mediated sleep disorders have been recognized in various conditions. Due to progressive muscle compromise, patients with muscular dystrophies and comorbid cardiomyopathies have demonstrated Cheyne-Stokes breathing with sleep.<sup>67</sup> Periodic breathing and prominent central sleep apnea has also been recognized in patients with cervical spinal cord injury and myotonic dystrophy—and while this can appear similar to Cheyne-Stokes pattern, the underlying mechanism

is not the same and is proposed to be due to instability in the control of breathing.<sup>68–70</sup> Further, patients with more advanced myotonic dystrophy have been recognized to have significant daytime hypersomnia out-of-proportion to their sleep-disordered breathing and REM at onset of sleep.<sup>71,72</sup> These can be characteristics associated with patients with narcolepsy and loss of hypocretin neurons, and it has been demonstrated that these patients can have low hypocretin-1 levels when their cerebrospinal fluid is sampled.<sup>72</sup>

### Restless leg syndrome

While most attention is directed against breathing and ventilatory sleep disorders in NMD patients, it is important to recognize that other pathologies may disturb sleep. Restless leg syndrome (RLS) is generally defined as presenting with the following features: (1) an urge to move the limbs that is usually associated with paresthesia or dysethesia; (2) symptoms that start or worsen with rest; (3) some relief of symptoms with physical activity; (4) symptoms worst at night; (5) can often be associated with periodic leg movements in sleep.<sup>73</sup> A wide array of conditions have been found to be associated with the presence of RLS including Parkinsonism, peripheral neuropathies, spinal cord injury, cognitive dysfunction, hyposmia, and cardiometabolic diseases.<sup>74</sup> In chronic neuropathic conditions, several populations of patients have been found to have a high prevalence of comorbid RLS. In patients with post-poliomyelitis, the rate of RLS is high, with the larger-cohort studies estimating prevalence ranging from 36–40.4%.<sup>75,76</sup> Similarly, patients with Charcot-Marie-Tooth type 2 disease have been found to have equally high rates of RLS.<sup>77</sup> As such, screening for the typical symptoms of RLS should be performed in these patients.

## Evaluation of sleep disorders in neuromuscular disease

### Symptoms

Many of the symptoms associated with sleep disorders in patients with NMD are similar to other patients, and others are unique. Patients will often present with daytime symptoms of morning headaches, daytime sleepiness, generalized fatigue, dyspnea bending over (or otherwise compromising diaphragm function by changing chest wall compliance), and excessive sleep time; while at night they may report frequent awakenings, orthopnea, snoring, nocturia, and potentially witnessed apneas.<sup>78–81</sup>

### Laboratory and clinical evaluation

All patients with neuromuscular and chest wall disorders should have a thorough neurologic examination and evaluation of vital signs, including pulse oximetry. Laboratory evaluation can be helpful for assessment of hypoventilation (high serum bicarbonate, high pCO<sub>2</sub>); although, with recognition that nocturnal hypoventilation and hypercapnia can be present in the absence of daytime hypercapnia.<sup>82</sup> Full pulmonary function testing, including any available advanced testing of respiratory muscle strength, should be obtained and serially assessed (especially if clinical symptoms are present and progressive).<sup>83</sup> While the predictive ability of pulmonary function parameters for sleep-disordered breathing is not perfectly reliable, several useful suggestions have been described and are generally seen as an evident sign of significantly impaired respiratory muscle strength which could predispose to nocturnal hypoventilation and other forms of sleep-disordered breathing (forced expiratory volume in 1 second [FEV1] ≤40% predicted, forced vital capacity [FVC] <1–1.5 L, reduction in seated to supine vital capacity >25%, significant reductions in maximal inspiratory [MIP] or sniff nasal pressures [SNIP]).<sup>33,40,84–88</sup>

**Table 2: Suggestive clinical findings for sleep-disordered breathing in neuromuscular diseases**

Signs and Symptoms
Daytime hypersomnolence
Morning headaches
Dyspnea (especially with positions that disadvantage the diaphragm or reduce chest wall compliance)
Orthopnea
Nocturia
Excessive sleep time
Fragmented sleep
Witnessed snoring or apneas

Tests of respiratory muscle strength can be particularly useful in assessing patients at risk for hypoventilation. It has been recognized that significant reductions in maximal static inspiratory and expiratory pressures (MIP, MEP) can exist without obvious correlations to the degree of generalized muscle weakness.<sup>89</sup> Further, a proximal distribution of muscle weakness in myopathic patients has been shown to portend a greater risk of respiratory muscle weakness, and reduced MIP/MEPs were associated with worse pulmonary function, CO<sub>2</sub> retention, and higher rates of respiratory infections and failure.<sup>89,90</sup> The ratio of MIP and MEP can also be useful—especially in conditions affecting the diaphragm—where a reduction in MIP and relative preservation of MEP would be expected. The ratio of MIP:MEP can potentially be used as an alternative to supine testing when such positioning cannot be tolerated.<sup>91</sup>

Given the nature of the maneuvers, maximal static mouth pressures can be difficult to perform and/or unreliable, especially as patients develop severe weakness (air leak, submaximal efforts). An alternative assessment of inspiratory muscle strength is maximal SNIP. The sniff maneuver comes naturally to most people and can be a better quantitative and reproducible test than MIP. In several studies using esophageal balloons, it was found that maximal sniffs generally produced higher pressures and were less variable than MIPs, were representative of esophageal pressure, and accurately reflected inspiratory muscle strength.<sup>22,92-95</sup> In patients with ALS, the SNIP test is sensitive for the detection of weakness early in the disease, declines with disease progression, and remains feasible to do in patients with advanced disease who cannot perform other maneuvers.<sup>96</sup>

**Nocturnal/sleep assessment**

While limited modalities such as nocturnal pulse oximetry and home sleep testing can be valuable in suggesting the presence of sleep hypoventilation or more severe sleep-disordered breathing, its value can be limited in the full evaluation of a patient with a neuromuscular or chest wall disorder.<sup>97,98</sup> Given its increased ability to properly classify event types, determine sleep stage, determine arousal etiologies, assess for limb movements, and be used for treatment titrations, full overnight polysomnography is considered the gold standard when evaluating patients with neuromuscular and chest wall disorders.<sup>5,98-100</sup> Furthermore, there should be strong consideration of performing non-invasive CO<sub>2</sub> monitoring during overnight polysomnography given the additional information it can provide, especially when assessing for nocturnal hypoventilation (i.e., demonstration of

**Table 3: Clinical testing findings suggestive of sleep-disordered breathing in neuromuscular diseases**

Daytime testing
Reduction in spirometry (FEV1 ≤40% predicted, FVC <1–1.5L, >25% decline in supine VC)
Significant reduction in maximal inspiratory or sniff nasal pressures
Blood gas abnormalities (hypoxemia, hypercapnia)
Serum bicarbonate elevation
Nighttime testing
Hypoxemia on nocturnal pulse oximetry
Abnormal overnight polysomnography (gold standard)
Elevated non-invasive carbon dioxide levels (TC or ET pCO <sub>2</sub> )

*ET = end-tidal; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; pCO<sub>2</sub> = partial pressure of carbon dioxide; TC = transcutaneous; VC = vital capacity.*

prolonged or cumulative elevations in CO<sub>2</sub>). There are two main options for non-invasive CO<sub>2</sub> monitoring: end-tidal CO<sub>2</sub> breath analysis and transcutaneous CO<sub>2</sub> analysis. Given potential issues with the validity of end-tidal CO<sub>2</sub> monitoring in patients with comorbid heterogenous ventilation and/or increased physiologic deadspace, transcutaneous CO<sub>2</sub> monitoring generally is preferred.<sup>101-104</sup>

A summary of the above clinical assessment is displayed in *Tables 2 and 3*.

**Treatment**

While continuous positive airway pressure is most often used in the general population for sleep apnea, it generally is not indicated for use in NMD-related sleep disorders due to the predominance of central events and hypoventilation. Furthermore, although significant nocturnal hypoxemia may be present, in these disorders it is secondary to hypoventilation and simple oxygen supplementation is not used as a standalone therapy.<sup>84,105</sup> In fact, institution of oxygen therapy alone could be deleterious.<sup>106</sup> As such, non-invasive positive pressure ventilation (NPPV) is the treatment of choice in these patients.<sup>107</sup> Several studies have demonstrated that NPPV improves survival in various NMDs, improves blood gas abnormalities, and improves quality of life and symptoms.<sup>108-116</sup>

More recently, several new modes have been developed that theoretically improve upon standard NPPV. Average volume-assured pressure support (AVAPS) and intelligent volume-assured pressure support (iVAPS) are proprietary modes that aim to maintain an overall target ventilation, namely tidal volume (AVAPS) or alveolar ventilation (iVAPS). In turn, the intended goal is to maintain a stable level of ventilation, and thus pCO<sub>2</sub>. These modes are likely well-suited to patients with neuromuscular and chest wall disorders whose respiratory efforts may vary significantly over time between sleep stages, changes in body position, and/or while awake. For example, since many patients have more prominent hypoventilation in REM, fixed pressure NPPV may provide too much pressure in some sleep stages and too little in others.<sup>117</sup> Several small studies have been performed assessing for improvements in patient comfort, adherence, and improvements in physiologic variables, which generally have supported their use in hypoventilatory conditions.<sup>118-122</sup> However, it should be noted that no large studies have demonstrated superiority of these new modes over standard NPPV—especially in terms of objective outcomes such as functionality or survival—and further research is needed to buttress their theoretical benefit.



## Indications for initiating treatment

There is some concern that current guidelines for the initiation of non-invasive ventilation in NMD patients may lead to a late initiation of treatment and further refining of guidelines may be needed to recommend the optimal period to maximize benefit.<sup>123</sup> This may be especially true in certain disease processes (e.g. ALS) where the early initiation of non-invasive ventilation may lead to improvement in lung function and quality of life.<sup>124,125</sup>

Published consensus guidelines suggest initiating non-invasive ventilation when: (1) vital capacity <50% predicted; (2) MIP <60 cm H<sub>2</sub>O; (3) nocturnal hypoxemia <88% for >5 minutes; or (4) daytime blood gas showing pCO<sub>2</sub> >45 mmHg.<sup>126</sup> More recently proposed guidelines expand these criteria to include symptoms related to muscle weakness (dyspnea, tachypnea, orthopnea, sleep arousals, morning headaches, daytime fatigue/sleepiness), clinical signs (use of accessory respiratory muscles, paradoxical respiration), and abnormal pulmonary function tests (forced vital capacity <80% predicted, SNIP <40 cm H<sub>2</sub>O, nocturnal desaturation, morning blood gas pCO<sub>2</sub> >45 mmHg).<sup>86</sup> As stated previously, the onset of nocturnal hypoventilation may significantly pre-date the emergence of the parameters above and it is likely that further modification of these criteria may include sleep-related data.

## Diaphragmatic pacing

In patients with an intact peripheral neuromuscular anatomy related to the major inspiratory muscles/diaphragm (high cervical spinal cord injury,

central ventilation disorders), it may be possible to provide significant inspiratory support by stimulating the diaphragm to contract—lessening, or even obviating, the need for assisted ventilation. This can be achieved by electrically stimulating the phrenic nerve or the diaphragm itself. In properly selected patients, these devices enable many individuals to reliably remain off assisted ventilation during the day, and many full-time for extended periods of time.<sup>127–129</sup> It is important to note that patient selection is extremely important, as there is a suggestion of potential harm in certain populations (e.g. ALS).<sup>130,131</sup>

## Conclusion

NMDs and chest wall disorders exhibit a complex array of respiratory physiologic changes that typically progress over time. As this occurs, reduced lung volumes and hypoventilation, due to respiratory muscle weakness, can promote significant abnormalities during sleep, leading to decreased quality of life, significant daytime symptoms, and overall worse survival. Practitioners caring for these patients should have a high index of suspicion for the emergence of sleep-related disorders, especially since ventilatory issues during sleep can precede awake ones. Patients should undergo a thorough clinical and laboratory work-up and be referred early for sleep evaluation with overnight polysomnography. NPPV is the standard treatment for sleep-disordered breathing in these patients and has been shown to promote a wide range of positive outcomes. □

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