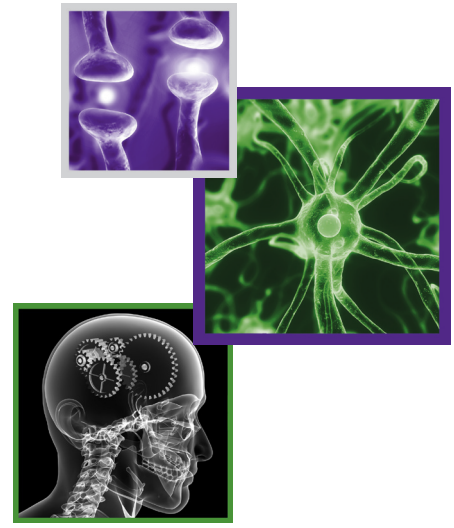
REVIEW

Sleep–wake problems in patients with amyotrophic lateral sclerosis: implications for patient management



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Practice Points

- Sleep–wake problems in patients with amyotrophic lateral sclerosis (ALS) are common, although they are unrecognized and understudied.
- The frequency of poor sleep increases with disease progression, especially because of the invariable involvement of respiratory muscles and the diaphragm, and normal rapid eye movement sleep-related changes in ventilation are magnified as a result of muscle weakness.
- Sleep disorders may also be the consequence of comorbid psychiatric conditions (i.e., anxiety and depression), spasticity, pain, choking, sialorrhea, poor secretion clearance, fasciculations, cramps, nocturia and reduced mobility.
- Sleep disturbances in ALS include insomnia, obstructive and/or central sleep-disordered breathing, nocturnal alveolar hypoventilation and restless legs syndrome (RLS).
- Insomnia in patients with ALS should be treated in a multifaceted approach, considering both pharmacological and nonpharmacological treatment. Additional caution should be used in patients with substantial respiratory muscle weakness not receiving ventilatory support.
- Sleep-disordered breathing can be effectively treated with noninvasive ventilation, and hence, all patients with ALS should be carefully and repeatedly evaluated using specific diagnostic tests such as nocturnal oximetry and/or polysomnography.
- RLS can be a cause of poor sleep in patients with ALS. When moderate or severe, RLS can disrupt sleep, thus causing daytime dysfunction. The diagnosis of RLS in patients with ALS could be challenging, especially for physicians unfamiliar with sleep-related disorders. RLS must be carefully distinguished from many mimic conditions such as neuropathic pain syndromes, leg cramps and spasms, stiffness and discomfort from spasticity or prolonged fixed position.

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SUMMARY Sleep–wake problems are frequent, although unrecognized, complications of amyotrophic lateral sclerosis (ALS). Sleep disorders such as insomnia, sleep-disordered breathing and restless legs syndrome have all been reported in patients with ALS, despite the limited number of studies and the small populations investigated so far. Sleep disturbances gradually worsen with disease progression, suggesting a relationship between the severity of disease and the neurodegenerative process. However, poor sleep can also be a consequence of several disturbances such as anxiety, depression, pain, choking, sialorrhea, fasciculations, cramps, nocturia and the inability to get comfortable and move freely in bed. Sleep disorders may have many reflections on patients with ALS, including excessive daytime somnolence, fatigue, impaired cognition, reduced quality of life and survival. This article reviews the recent literature on sleep–wake problems in patients with ALS, focusing on the implications for patient management.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord, leading to muscle atrophy, paralysis and death because of respiratory failure within 2–5 years, even though approximately 10% of ALS patients survive for 10 or more years [1].

Although it is well known that patients with ALS frequently report sleep-related complaints (e.g., insomnia, disturbed sleep, frequent nocturnal awakenings, nightmares, morning headaches and daytime sleepiness), these symptoms have usually been ascribed to disturbed nocturnal gas exchange and hypoventilation [2,3]. As a result, sleep disturbance is among the least studied aspects of ALS and, in the clinic, generally receives little attention from most neurologists. It has really only been in the last two decades that investigation has been directed towards understanding the nature and pattern of sleep disturbances in ALS, especially those related to sleep-disordered breathing (SDB) and nocturnal hypoventilation. This article reviews the recent literature on sleep–wake problems in patients with ALS, focusing on the implications for patient management.

How common are sleep disturbances in ALS?

A recent case–control survey from our group suggests that sleep disturbances occur in 59% of patients with ALS, and 28% reported moderate-to-severe dysfunction [4]. In 42%, sleep complaints appeared after disease onset, and the most common sleep problems reported were nocturia (54%), difficulties staying asleep (48%), nocturnal cramps (45%), snoring (33%) and difficulties falling asleep (32%). Twenty three patients (23%) reported excessive daytime sleeping, and 52 (52%) patients complained of difficulties turning in bed. Patient disability was the most important variable associated with poor sleep quality [4].

In another case series study on 24 patients with ALS, it was found that insomnia symptoms were present in 25% of patients, and patients in a terminal state had a higher frequency of sleep disturbances (up to 48%) [5].

Ferguson and colleagues reported that most of the patients included in their small case series study complained of difficulty initiating and maintaining sleep (71 and 100%, respectively) [6].

SDB can be observed in patients with ALS, especially in the advanced phase of the disease. Mild-to-moderate obstructive sleep apnea (OSA) cases have been reported in some observational studies, as well as central apneas, while nocturnal hypoventilation, primarily related to pathology in the cervical spinal cord α-motor neurons, increases as the disease progresses [4,6–15].

In our experience, however, only a minority of patients complained about their sleep problems spontaneously, while the majority complained when asked [4].

In line with the aforementioned findings, polysomnographic examinations usually show abnormalities such as increased frequency of SDB, reduced sleep efficiency, fragmented sleep architecture with reduced slow wave sleep, as well as reduced and fractured rapid eye movement (REM) stages, and frequent arousals [4,6,10,12].

The nature of sleep disturbance in ALS

The most frequent sleep disturbances in patients with ALS are insomnia, excessive nocturnal motor activity and SDB. Other, less studied, possible causes of sleep–wake disturbances are circadian rhythm disorders (CRDs) and REM sleep behavior disorder (RBD).

Insomnia

Insomnia occurs when patients, despite adequate opportunity, have trouble with sleep initiation (initial insomnia), sleep maintenance (middle insomnia), or arising earlier than desired (terminal insomnia), coupled with impaired daytime functioning. Patients could also experience unrefreshing sleep, that is, feeling tired and sleepy after waking in the morning [16].

The prevalence of insomnia with daytime impairment may range, in the general population, from 10 to 15%, and from 30 to 100% in patients with neurodegenerative diseases [17]. In our recent survey, the prevalence of initial insomnia in the population of patients with ALS was 32%, the prevalence of middle and terminal insomnia was 48%, and unrefreshing sleep was reported by 29% of patients [4].

Physicians should be aware of common symptoms seen in ALS that may precipitate insomnia. Indeed, nocturia and difficulties turning in bed can cause early morning awakening, disturbed sleep and increased sleep fragmentation. Muscle cramps, spasticity, pain, and restless legs syndrome (RLS) symptoms may cause difficulty in initiating and maintaining sleep, and SDB can fragment sleep architecture and cause daytime somnolence. Patients with bulbar impairment could also present problems with choking, sialorrhea and poor secretion clearance [4,6,18].

Moreover, the role of psychiatric conditions, such as anxiety and depression, in determining insomnia should not be underestimated [19]. Polypharmacy could also be a cause of secondary insomnia in patients with ALS. Although there is no known direct effect of riluzole on sleep function, this drug may induce slight somnolence and it has also been shown to increase slow-wave sleep in rats [20–22]. Moreover, many of the medications that are prescribed for medical conditions that could co-occur in patients with ALS may also contribute to, or even cause, insomnia, such as antihypertensives, respiratory medications, chemotherapy, hormones or psychotropics (e.g., selective serotonin-reuptake inhibitors, atypical antidepressants and monoamine oxidase inhibitors) [23,24]. **Figure 1** summarizes the many potential contributing factors that may cause insomnia in patients with ALS.

Circadian rhythm disorders

CRDs can occur from a mismatch between the internal interval and the external environment regarding the timing and duration of sleep [16].

The prevalence of CRD in the general population is unknown, and, at present, there is no study that specifically investigated the possibility of higher rates of CRD in patients with ALS, or supporting an association or a causal relationship between the two conditions. However, as people age, their circadian rhythms become weaker, desynchronized and lose amplitude [24]. It could be speculated that the degenerative process, as seen in ALS, could contribute in disrupting the function of the biological pacemaker. Moreover, the external cues that are necessary to entrain the circadian rhythm of sleep–wake cycles may be weak or missing in patients with ALS, especially in advanced phases of the disease. Patients with ALS may also have a reduced time-of-light exposure because of their physical limitations and this could have an effect on the circadian rhythm of their sleep–wake cycles. Other possible causes of CRD may also be present in patients with ALS, as well as in other populations of similar age [24], although these should be differentiated from irregular sleep–wake cycles (named 'sundowning') observed in patients with Alzheimer's disease.

RLS & periodic limb movements in sleep

RLS is a disorder with sensory and motor components. The International Restless Legs Syndrome Study Group established four essential clinical criteria defining RLS:

- An urge to move, usually due to uncomfortable sensation in the legs;
- The urge in the legs improves with movement of the legs;
- Symptoms worsen at rest;
- Symptoms often worsen in the evening or at night [25].

When severe, RLS disrupts sleep, causing excessive daytime sleepiness, depression, insomnia and fatigue [26]. In the general population, RLS frequency varies from 5 to 10%, but increased RLS frequency (up to 55% of cases) has been reported in many neurodegenerative disorders such as Parkinson's disease, spinocerebellar ataxias, Huntington's disease and hereditary spastic paraparesis [27]. Severe RLS is associated with significant sleep loss with patients reporting as little as 3–5 h, thus, causing sleep deprivation and daytime dysfunction.

In a recent case–control study, we found an increased frequency of RLS in a population of

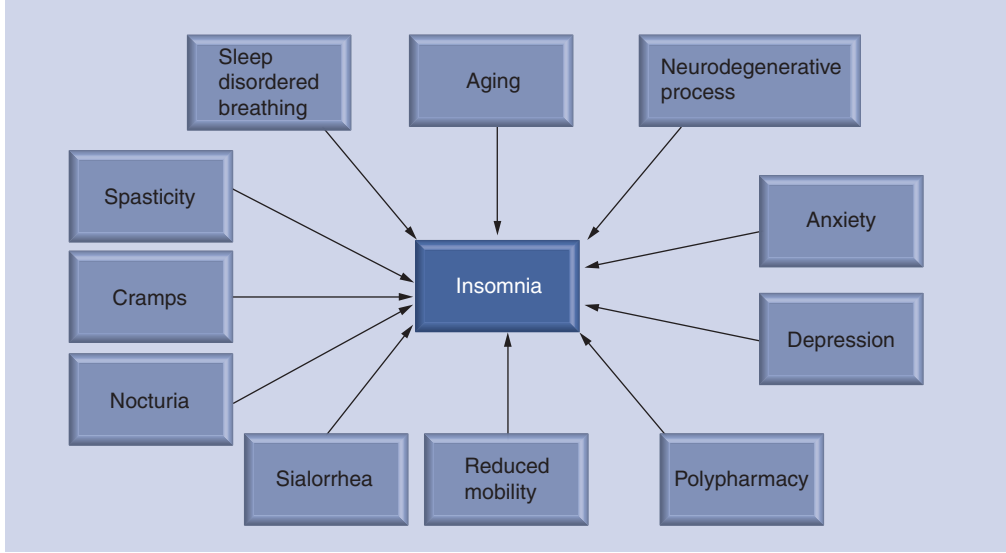

Figure 1. Contributing factors that may cause insomnia in patients with amyotrophic lateral sclerosis.

76 patients with ALS. RLS was present in 25% of patients (and in 8% of age- and sex-matched controls), and patients with ALS and RLS demonstrated a shorter history of RLS complaints and a higher frequency of symptom occurrence [28]. Moreover, patients with ALS and RLS frequently reported insomnia complaints and showed increased functional disability. Iron status was within the normal range [28].

Another group also confirmed the increased frequency of RLS symptoms in patients with ALS (18.8%), and they suggested that this relationship may be mediated by reduced mobility, which would aggravate the sensation of motor restlessness, normally relieved by movement [29].

It should be noted, however, that distinguishing RLS from other motor and sensory symptoms in ALS can be challenging since patients with ALS often complain of leg spasms and cramps or leg discomfort, which is worse after immobility. Additional RLS mimics that must be excluded are neuropathic pain syndromes, leg cramps and spasms, stiffness from spasticity or prolonged fixed position. In these cases, it is important to make sure that the patient feels a discomfort in the affected limb, that the movements of the limbs are voluntary, bring at least some relief, and are maximal in the evening or at night [30,31]. Moreover, in case of doubt, a polysomnographic assessment, showing increased periodic leg movements in sleep, could be of help.

■ REM sleep behavior disorder

RBD is a parasomnia in which the skeletal muscle atonia, normally found in REM sleep, is absent, replaced by increased electromyographic tone on submental or limb leads. As a consequence, patients with RBD exhibit injurious or disruptive behavior in REM sleep, and may act out their dreams. Although RBD can be idiopathic, it frequently arises secondary to a neurological disease with brainstem involvement, most commonly α-synucleinopathies, with a prevalence ranging from 40 to 100% [32]. Excluding three single cases reported in the literature [33,34], there are, at present, no studies that specifically examined abnormal motor activity during sleep that could be indicative of RBD in patients with ALS.

■ Sleep-disordered breathing

SDB, including OSA, central sleep apnea and nocturnal hypoventilation, are a group of disorders characterized by disordered respiration during sleep [35]. OSA is characterized by repetitive episodes of cessation of breathing (apneas) or partial upper airway obstruction (hypopneas) in the presence of respiratory effort, that are often associated with reduced blood oxygen saturation. Hypoventilation is defined by an abnormally elevated $PaCO_2$ and high serum bicarbonate levels with an associated reduction of PaO_2. SDB is a common respiratory diosorder, affecting 2–4% of adults. Its prevalence increases with age (especially OSA), and it has also been frequently reported in patients with

neurodegenerative disorders such as multiple system atrophy or Alzheimer's disease [36].

Patients with SDB may present with daytime sleepiness, unrefreshing sleep, morning headache, nocturnal apneas, gasping, choking, snoring, fatigue, poor concentration, mood changes and nocturia – all complaints frequently experienced in ALS.

SDB is common in ALS with the progression of the disease, owing to the result of progressive involvement of respiratory muscles (particularly the diaphragm). However, SDB can occur even when respiratory muscle function is only mildly affected and patients present normal daytime gas exchange [6,10,37]. Moreover, a proportion of patients, although exhibiting a normal diaphragmatic function, may show mild periodic oxygen desaturations during sleep, which could represent an early sign of impaired central neural control of respiration or diaphragmatic fatigue [12]. Nocturnal hypoventilation is the most common form of SDB in ALS, representing a relevant milestone in the natural history of this illness, and causing severe sleep fragmentation and daytime sleepiness. Nocturnal hypoventilation is particularly severe during REM sleep, when all postural and accessory muscles are physiologically atonic, and only the diaphragm, which may itself be impaired, is left to sustain ventilation and overcome any upper airway resistance [6].

Sleep apnea seems to occur less frequently than hypoventilation, but there is no agreement on its prevalence, since some observational studies reported high rates of OSA in patients with ALS, whereas others have found the opposite [4,6,10,11,37,38]. Bulbar impairment, however, has not been related to the increased risk of OSA, probably because of the inability of patients with respiratory muscle weakness to generate an inspiratory pressure greater than the upper airway closing pressure [6]. On the other hand, some authors observed central apneic events more frequently, and they related this finding to respiratory muscle weakness, especially during REM sleep [6,8,10,11,38].

Since nocturnal oximetry is easily performed and can be executed domiciliary, it is commonly used in clinical practice for the evaluation of respiratory involvement in patients with ALS, to predict survival, and as a guide to initiate mechanical ventilation [39–44]. Pulmonary function parameters, such as sniff nasal inspiratory pressure and capnography, could also be useful to detect SDB in these patients [45,46].

Consequences of poor sleep

Although the consequences of poor sleep in patients with ALS have not yet been extensively investigated, poor sleep may lead to excessive daytime sleepiness, which results from multiple and recurrent nighttime arousals that cause sleep fragmentation [24]. Other common manifestations of the daytime sleepiness include unintentional napping and falling asleep at inappropriate times during the day, causing social and occupational difficulties as well as reduced vigilance [24]. Excessive daytime sleeping has also been linked to increased risk of falls, cognitive dysfunction and impaired memory [47,48].

Sleep disturbances could cause a decreased quality of life, and could be responsible for psychiatric symptoms such as anxiety and depression [24].

Furthermore, poor sleep has recently been associated with fatigue, especially in the presence of nighttime complaints such as nocturia and muscle cramps [49]. As in other neurological disorders known to be associated with sleep complaints (e.g., multiple sclerosis, α-synucleinopathies or tauopathies), sleep disturbances could result in a potential increase in disability, although this has not yet been proven in large studies.

Finally, respiratory impairment and nocturnal hypoventilation are associated with reduced survival, and there is considerable evidence that noninvasive ventilation (NIV) could be useful to alleviate respiratory symptoms, to extend survival, and to improve quality of life and cognitive functions in most patients [41,50–58].

Assessment & treatment of sleep disturbances in ALS

■ Treatment of insomnia

Insomnia in patients with ALS should be treated in a multifaceted approach, considering different possible therapies that should be tailored to the single patient's needs.

Treatment options for insomnia include basic sleep hygiene education, psychological and behavioral interventions and pharmacotherapy. Sleep hygiene education is intended to provide information regarding lifestyle (i.e., diet, exercise, alcohol and caffeine intake) and environmental factors (i.e., light, noise and temperature) that may either interfere with, or promote, better sleep [59,60]. Psychological and behavioral therapies for insomnia include sleep restriction, stimulus-control therapy, relaxation training,

cognitive strategies, and a combination of those methods, referred to as cognitive behavioral therapy [17]. Although there are many studies attesting that patients with primary insomnia benefit from these treatments [61], at present, there are no studies that have specifically investigated the effects of nonpharmacological approaches on insomnia complaints in patients with ALS.

With regards to pharmacotherapy, despite the high frequency of sleep complaints in our ALS population, we observed a relatively low use of sleeping medications, which was comparable to that of healthy controls [4]. We related this finding to the low rate of patients spontaneously reporting sleep–wake problems, but we also inferred that a cautious approach from physicians, concerned about possible negative effects of hypnotics on respiratory function, could have also played a role [4]. Pharmacological intervention should only be introduced if required, and if the sleep disorder is comorbid with a medical or psychiatric condition such as pain, depression, anxiety or RLS, the underlying disease has to be treated [17]. Regarding sleep medications, there are ten medications approved by the US FDA for the treatment of insomnia (Table 1). Besides the careful consideration of side effects (e.g., sedation, daytime sleepiness, rebound insomnia, addiction, tolerance, risk of falls and cognitive impairment), these drugs should be used with additional caution in patients with substantial respiratory muscle weakness not receiving ventilatory support, because of their potential to reduce ventilation [17,62,63].

Other drugs frequently used to treat insomnia are sedating antidepressants such as trazodone, amitriptyline, doxepin and mirtazapine, particularly for sleep-maintenance insomnia, and in patients with comorbid depression [64]. However, it must be noted that treatment of severe mood instability in the context of insomnia should be treated separately and independently for better long-term efficacy and reduction of relapse of either sleep or mood condition. Moreover, additional caution should be posed to the anticholinergic side effects such as dry mouth, constipation, urinary retention and confusion.

Treatment of SDB

The most common and proven treatment of SDB in ALS is NIV. Continuous positive airway pressure is the preferred appliance in the case of OSA, however, since the most common disturbance in ALS is nocturnal alveolar hypoventilation, patients are usually started with nocturnal bilevel positive airway pressure ventilation. All patients with ALS can benefit from NIV therapy, and a trial with this appliance should never be discouraged, even if some authors have concerns that marked bulbar involvement could be associated with reduced tolerance and maybe survival [51,53]. As in other patient populations, NIV compliance could be an issue, but our group has recently demonstrated that intensive educational training and adaptation on NIV, when performed in a hospital multidisciplinary setting, increases compliance and tolerance over time, even in those patients with severe bulbar impairment [65]. NIV could improve sleep architecture, daytime sleepiness, self-reported

Table 1. US FDA-approved hypnotics for insomnia.

Name of the agent	Dose (mg)	Half-life (h)	Duration	Indications
Benzodiazepines				
Flurazepam	15–30	48–120	L	Initial, middle and/or terminal insomnia
Quazepam	7.5–15	41	L	Initial, middle and/or terminal insomnia
Estazolam	1–2	10–24	I	Middle and/or terminal insomnia
Temazepam	7.5–30	3.5–18	I	Middle and/or terminal insomnia
Triazolam	0.125–0.5	1.5–5.5	S	Initial insomnia
Nonbenzodiazepines				
Zaleplon	10	0.9–1	S	Initial insomnia
Zolpidem	5–10	2.5	S/I	Initial insomnia
Zolpidem ER	12.5	2.8	S/I	Initial and/or middle insomnia
Eszopiclone	2–3	6	I	Initial and/or middle insomnia
Melatonin receptor agonists				
Ramelteon	8	1.2–6	S	Initial insomnia

ER: Extended release; I: Intermediate acting; L: Long acting; S: Short acting.

symptoms such as snoring, choking, and gasping, could ameliorate cognitive impairment, could improve nocturia complaints, reducing the number of voids per night. Moreover, NIV reduces or eliminates OSA and nocturnal oxygen desaturations, thus ameliorating and supporting respiratory function.

■ Treatment of other sleep disturbances

Although no evidence-based treatment exists for RLS in patients with ALS, if RLS is documented it should be treated with a dopamine agonist as first-line therapy. Pramipexole and ropinirole are both FDA-approved for the treatment of RLS in the general population, although physicians should pay attention to the potential risk of augmentation (i.e., the worsening of RLS symptoms with an earlier occurrence in the evening or an increase in symptom severity), that is a class-specific and very potentially dangerous aspect of the dopamine-agonists treatment. Other non-FDA-approved therapies for RLS include the use of opioids, gabapentin and benzodiazepines. Moreover, when the patient's ferritin is less than 45–50 µg/l, oral iron treatment is usually indicated as a supplemental treatment [66].

The goal of therapy for CRD is to resynchronize the circadian clock with the desired 24-h light–dark cycle. For these patients, chronotherapy, phototherapy and melatonin could be tried, since they have been employed in the general population to shift the circadian rhythm back to a normal range [24].

The first-line therapy for treating RBD is clonazepam (0.5–1 mg at bedtime). Although its specific mechanism of action in RBD is unknown, clonazepam is effective in almost every patient, with little evidence of tolerance or abuse. However, caution is needed regarding side effects, including sedation and the potential for respiratory depression. On the other hand, selective serotonin-reuptake inhibitors and other antidepressants can precipitate RBD symptoms, and should be avoided.

Conclusion & future perspective

Sleep–wake disturbances are common complications in ALS that should be recognized promptly as they are associated with significant morbidity and can be successfully treated. However, the prevalence and strength of this association has not been determined on a large-scale level, and there are still a small number of studies dealing with this subject. Moreover, there is a relative lack of objective reports or polysomnographic data. Most of these knowledge gaps, in our opinion, are the reflection of the limited knowledge and the reduced expertise in sleep medicine of many physicians directly involved in the care of patients with ALS (i.e., neurologists and pulmonologists). However, as it has been the case in Parkinson's disease, sleep dysfunction, as well as other nonmotor symptoms, could gain increasing attention and clinical value in the scientific community as larger evidence is gathered.

Among the areas of interest that could deserve more attention in future studies, particular relevance should be devoted on the specific contribution of the various clinical pictures characteristic of the disease. In particular, investigating the different roles of bulbar dysfunction (causing sialorrhea, drooling and dysphagia) and upper and lower motor neuron involvement (responsible for spasticity, reduced mobility, fasciculations and cramps) on nighttime complaints could reinforce our knowledge in this subject, and provide interesting insights with potential positive reflections on the clinical management of these patients.

Moreover, although they have not been specifically tested in patients with ALS so far, some recently introduced diagnostic and treatment devices, such as ambulatory polysomnographic monitoring, actigraphic devices, auto servo-ventilation and autocontinuous positive airway pressure devices, as well as smart phone applications, could be implemented in the near future for treating and monitoring patients with ALS.

Further studies are also needed to investigate the causes of disturbed sleep in ALS. Neurodegenerative diseases result from progressive deterioration of neuronal cells that may eventually lead to CNS-related dysfunction including sleep disorders, and ALS is no exception. Therefore, the pathogenesis of sleep disturbances may be secondary to direct structural alterations of neurons and networks regulating sleep–wake cycles, but could also be an indirect consequence of several disturbances such as anxiety, depression, spasticity, pain, choking, sialorrhea, poor secretions clearance, fasciculations, cramps, nocturia and the inability to get comfortable and move freely in bed [4,6].

Finally, additional work by our group is focused in identifying the reflections of sleep abnormalities on quality of life and the impact of their optimal management on the patients and their caregivers.

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