Treating restless legs syndrome in the context of sleep disordered breathing comorbidity

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ABSTRACT Obstructive sleep apnoea (OSA) and restless legs syndrome (RLS) are two of the most prevalent sleep disorders and can coexist within the same patient. Nonetheless, the recognition of RLS among OSA patients has important clinical implications, since RLS can disrupt sleep despite adequate treatment of sleep disordered breathing and should be treated accordingly. Furthermore, the presence of OSA can also increase the severity of RLS. Therefore, it is important to be able to correctly identify both disorders and treat them effectively. The present article reviews our current knowledge on this comorbidity and discusses potential treatment options for RLS in the context of OSA.

Introduction

Both obstructive sleep apnoea (OSA) and restless legs syndrome (RLS) are considered to be among the most common sleep disorders [1–5]. However, it is unclear whether there is a causal association between both disorders. Identifying RLS in OSA patients is relevant, particularly because RLS can contribute to sleep fragmentation despite adequate treatment of sleep disordered breathing. In addition, the presence of RLS can make adjustment to continuous positive airway pressure (CPAP) treatment more difficult, and should be treated accordingly [6].

In this article, we will review current knowledge of RLS its relationship with sleep disordered breathing. The evidence on the effects of treatment of RLS on OSA, and treatment of OSA on RLS, are also discussed.

RLS in sleep disordered breathing

RLS is not only a common neurological movement disorder, but also one of the most common causes of sleep disturbance. It affects up to 10% of the general adult population and can be severe in up to 2–3%. Nevertheless, it still remains an underdiagnosed condition [7, 8].

RLS patients frequently present with difficulties initiating and/or maintaining sleep, as RLS is more common during the evening or night. It is mainly characterised by neurosensory symptoms in the form of strong urge to move the limbs frequently associated to distressing paraesthesia-like sensations [9, 10], and is typically associated to periodic leg movements of sleep (PLMS) when assessed by means of polysomnography [11].

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RLS typically manifests when the patient is at rest; immobility or relaxation are associated with a greater likelihood of symptom occurrence. Conversely, symptoms usually improve or resolve when the patient initiates physical activity; when symptoms arise patients will experience an intense urge to move in order to relieve the discomfort felt.

Genetic, environmental and medical factors provide a variable expression of RLS symptoms. These symptoms vary considerably in frequency from being occasional to daily, while severity ranges from mildly annoying to fully disabling. Furthermore, symptoms fluctuate widely in its intensity over time and may even remit for differing periods of time.

The diagnostic definition of RLS is based on expert consensus and was first developed in 2003 following a workshop at the National Institutes of Health. However, a more recent update improves specificity by excluding mimics. Thus, RLS is currently diagnosed by ascertaining the presence of five essential clinical criteria (table 1) [9].

Surprisingly, not many studies have examined the prevalence of RLS patients diagnosed with OSA to date [12]. However, one small prospective study [13] examined the prevalence of RLS in patients who had already been diagnosed with OSA by means of polysomnography. Screening for RLS was performed by means of a questionnaire and by a face-to-face interview which used established diagnostic criteria. Clinically significant RLS was found in 8.3% of OSA patients in contrast to 2.5% in the control group. However, no direct relationship was found between the severities of both disorders. In addition, a large European cross-sectional study interviewed nearly 20 000 subjects among the general population for RLS symptoms and found prevalences of 3.9% for PLMS and 5.5% for RLS, respectively [14]. An OSA diagnosis appeared to be predictive of PLMS and RLS.

Excessive daytime sleepiness in patients with OSA and RLS

Polysomnographic studies have shown that RLS patients with idiopathic RLS have fragmented sleep with long sleep latencies, shorter total sleep time and a higher arousal index compared with controls [15].

Moreover, an increased PLMS index is present in ~88% of RLS patients [11]. These PLMS can disrupt sleep and contribute to hypersomnia among OSA patients with comorbid RLS. It is conceivable that a combination of PLMS and OSA might lead to increased excessive daytime sleepiness. However, a retrospective study found that the combination of PLMS and OSA did not result in worsening hypersomnia compared with OSA patients without PLMS [16, 17].

One study, using both the multiple sleep latency test (MSLT) and the Epworth sleepiness scale, compared the severity of excessive daytime sleepiness among OSA patients with PLMS and without PLMS [18]. Before CPAP treatment, OSA with PLMS did not show greater sleepiness compared to OSA patients without PLMS. In another large study, which measured daytime sleepiness by means of MSLT, no association between the rate of periodic leg movements and subjective or objective sleepiness was found [17].

Periodic leg movements during sleep should be differentiated from movements caused at the end of respiratory events. Current international guidelines, based on preliminary empirical evidence, recommend to remove from scoring any candidate leg movement on which any part of the leg movement occurs between 2.0 s before and 10.25 s after the end of SDB events [19, 20].

Frontal changes and cardiovascular risk in RLS with OSA

Quality of life is reduced in patients with RLS, even when compared to other chronic medical conditions, and this is mainly due to the presence of sleep disturbance [21]. Indeed, sleep loss might be responsible for cognitive deficits caused by frontal lobe dysfunction [22]. Similar changes have been described in untreated OSA patients [23].

The risk of coronary artery disease and cerebrovascular disease is higher in patients with moderate-to-severe RLS compared with controls, even after controlling for age, sex, body mass index, diabetes, systolic blood pressure, antihypertensive medication use, cholesterol and smoking history [24].

Furthermore, RLS might be an independent risk factor for the development of cardiovascular diseases. It has been suggested that either the sleep disruption resulting from RLS or the increased number of periodic leg movements leads to arterial hypertension in RLS patients, thus facilitating an increase in the cardiovascular and/or cerebrovascular risk [25, 26]. The association of RLS and OSA could be additive and worsen even further the predisposition of each disease to promote adverse cardiovascular events.

Impact of treatment of sleep disordered breathing on RLS/PLMS

Periodic leg movements are commonly found both with OSA or upper airway resistance syndrome, and also following successful CPAP therapy. Indeed, it has been suggested that CPAP therapy can even induce

TABLE 1 Diagnostic criteria for restless legs syndrome (RLS)

Essential clinical criteria	
An urge to move the legs, usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs	Sometimes the urge to move the legs is present without the uncomfortable sensations. The arms or other parts of the body may also be involved in addition to the legs. Often the urge to move and the accompanying sensory symptoms are difficult to separate symptomatically or temporally. The sensations are described as painful in one-third of RLS patients.
The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting	When examined by means of objective tests, such as the multiple SIT, patients with RLS report pronounced sensory symptoms in the legs and the presence of PLMS while both resting and awake, and these increase with the duration of rest.
The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues	RLS patients feel at least some symptomatic relief right after the initiation of the activity. Usually, the simple act of moving or walking suffices. Symptoms should generally not return nor worsen as long as activity continues.
The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day	Patients with RLS should report fewer symptoms when resting in the morning than in the evening or night. The critical clinical question for this criterion involves ascertaining circadian differences in symptom response to rest. However, patients with very severe RLS may have relentless symptoms persisting throughout the day and night.
The occurrence of the above features is not solely accounted for by symptoms primary to another medical or behavioural condition (*e.g.* myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort or habitual foot tapping)	These conditions, often referred to as "RLS mimics", have been commonly confused with RLS.
Supporting features	These criteria are not essential, but can help to support the diagnosis.
Periodic leg movements	Periodic leg movements are repetitive, stereotyped flexor-withdrawal-like movements of the legs which occur during sleep. However, periodic leg movements can also occur during wakefulness. PLMS occur in ~80–89% of RLS patients seen in a clinic setting, and periodic limb movements during wakefulness occur with a similar same range of periodicity. Periodic leg movements occur with significant transient changes in EEG, heart rate and blood pressure, which may reflect an underlying process that produces an increased risk of cardiovascular disease which has been observed in RLS patients in several studies. Although PLMS are fairly specific to RLS, they are not very sensitive, as they do occur at lower rates with several other medical conditions, with many medications and are common among adults aged >45 years Periodic limb movement disorder is a sleep disorder characterised by an increased number of PLMS associated with insomnia, unrefreshing sleep or daytime hypersomnia after exclusion of other sleep disorders as a cause of these symptoms. In contrast, periodic leg movements during relaxed wakefulness, as measured by the SIT, have high sensitivity and specificity for RLS, particularly if evaluated multiple times and combined with subjective leg discomfort scores in the multiple SIT.
Dopaminergic treatment response	Most RLS patients show at least some initial clinical benefit to fast-acting dopaminergic medications, *e.g.* levodopa and dopamine agonists. Although a failure to respond to dopaminergic treatment should raise some concern about the accuracy of diagnosis, it does not necessarily exclude a diagnosis of RLS.
Family history	RLS has been noted to occur commonly in families, indicating significant genetic or shared environmental factors for the disease. In fact, the risk of RLS is nearly six times higher among first-degree relatives of RLS patients than among those without.
Lack of profound daytime sleepiness	Patients with moderate-to-severe RLS have chronic short sleep times, but generally do not report a level of daytime sleepiness that would be expected for the degree of sleep loss. They will usually have slightly elevated but still normal ESS scores. Thus, hyperarousal might be part of the pathophysiology of RLS. Profound sleepiness should prompt evaluation for another cause, such as sleep apnoea, narcolepsy or medication effect.

SIT: suggested immobilisation test; PLMS: periodic leg movements of sleep; EEG: electroencephalogram; ESS: Epworth sleepiness scale. Reproduced and modified from [9] with permission.

or worsen PLMS [27], and the effect of CPAP on PLMS may be related to the severity of the OSA: thus, patients with severe OSA experience an increase in PLMS during CPAP treatment, while patients with mild OSA show a decrease in PLMS.

PLMS may have various aetiologies during CPAP therapy; some could be spontaneous in patients with underlying periodic limb movement disorder, and be unmasked by CPAP therapy, whereas others could be induced by sleep disordered breathing, and as such improve with CPAP treatment [28–31].

Taken together, although the physiopathology of RLS/PLMS in relation to the treatment of sleep disordered breathing is multifactorial and still poorly understood, treatment of OSA with CPAP improves cardiovascular outcomes, and this could be beneficial for RLS/PLMS, given its cardiovascular effects [32].

Impact of RLS/PLMS on the treatment of sleep disordered breathing

Persistence of residual sleepiness despite adequate treatment and CPAP compliance is not uncommon in OSA patients [33]. In these patients, other factors than OSA might be at play.

Available data indicate that neither RLS nor PLMS contribute to the daytime sleepiness, and other causes of hypersomnia should be sought in these patients. However, RLS could be implicated in the residual fatigue experienced by some OSA patients despite effective CPAP therapy [17, 18, 34, 35].

Treatment of RLS in the context of OSA

In general, treatment for RLS should be initiated when the symptoms impair the patient's quality of life, daytime functioning, social functioning or sleep. In the context of comorbidity with OSA, any RLS symptoms that interfere with the treatment of OSA, *i.e.* making the use of CPAP more difficult should induce the initiation of a specific treatment [12, 36, 37].

Before any RLS treatment is initiated, it is important to first normalise iron stores. Thus, any measures (including oral or intravenous iron administration and prevention of blood losses) should be taken to ensure that ferritin levels are raised to >75 $ng \cdot mL^{-1}$. Recent guidelines on iron treatment for RLS recommend oral iron treatment for ferritin levels $\leqslant 75\ \mu g \cdot L^{-1}$ [38]. Oral iron is non-efficacious in iron-sufficient subjects, but its benefit for patients with low peripheral iron status has not been adequately evaluated.

For patients with ferritin $\leqslant 100\ \mu g \cdot L^{-1}$, or whenever oral iron is not appropriate, intravenous supplementation should be considered. No iron treatment is recommended if transferrin saturation is >45%.

Additional conservative measures include elimination of any medications that exacerbate RLS symptoms, such as antihistamines, dopamine antagonists, antinausea medications, antidepressants and lithium [36].

Two classes of drugs are frequently used for the treatment of RLS: dopamine agonists and $\alpha_2\delta$ ligands [36]. The first group includes pramipexole, ropinirole and rotigotine, all of which are US Food and Drug Administration (FDA)- and European Medicines Agency (EMEA)-approved (table 2) [36]. Dopamine agonists are effective in the treatment of subjective sensitive symptoms and PLMS. Their main side-effects are transient nausea, headache and somnolence, and in the case of the rotigotine patch, skin reactions. Nevertheless, although their short-term efficacy is very clear in most cases, the main long-term complications of dopamine agonists are augmentation of RLS symptoms, tolerance and impulse control disorders (ICDs) [39].

Augmentation is a worsening of RLS symptoms manifested by an earlier onset of symptoms in the afternoon or evening compared to before treatment initiation [40]. It consists of symptoms starting earlier

TABLE 2 Recommended doses for commonly used medications in restless legs syndrome

	Initial dose	Maximum dose
Pramipexole	0.125 $mg \cdot day^{-1}$	0.50 $mg \cdot day^{-1}$
Ropinirole	0.25 $mg \cdot day^{-1}$	4 $mg \cdot day^{-1}$
Rotigotine patch	1 $mg \cdot day^{-1}$	3 $mg \cdot day^{-1}$
Gabapentin enacarbil	600 $mg \cdot day^{-1}$	1200 $mg \cdot day^{-1}$
Pregabalin	75 $mg \cdot day^{-1}$	450 $mg \cdot day^{-1}$
Gabapentin	300 $mg \cdot day^{-1}$	2400 $mg \cdot day^{-1}$
Methadone	5–10 $mg \cdot day^{-1}$	20–40 $mg \cdot day^{-1}$
Oxycodone/naloxone	5 mg oxycodone/ 2.5 mg naloxone twice daily	20 mg oxycodone/ 10 mg naloxone twice a day
Clonazepam	0.25 $mg \cdot day^{-1}$	2 $mg \cdot day^{-1}$

in the afternoon, a spread of symptoms to previously unaffected body parts (*i.e.* the arms) or symptoms arising more quickly following immobility. It can occur at any time during treatment, but is usually more likely with higher doses and drugs with shorter-acting half-lives. One study found that up almost 75% of treated patients suffered from some degree of symptoms of augmentation [41].

ICDs have been reported to develop in up to 17% of patients with RLS undergoing treatment with dopamine agonists [42]. ICDs are likely to increase with higher doses of dopaminergic agents and in females.

Surprisingly, the effect of dopaminergic drugs on sleep disordered breathing has rarely been investigated. One study found a marginal improvement of the apnoea–hypopnoea index in patients undergoing a 3-week treatment with 0.09–0.54 mg pramipexole for sleep bruxism [43].

Given the potential for a worsening of RLS symptoms following long-term treatment with dopamine agonists, most current expert guidelines recommend keeping their dose at a minimum, and if possible, initiating treatment with a non-dopaminergic agent [36].

The main alternatives to dopamine agonists are $\alpha_2\delta$ ligands of the calcium channels, such as gabapentin or pregabalin. None of these drugs are FDA- or EMEA-approved, but gabapentin enacarbil, a prodrug of the former, is approved in the USA and in Japan. Their mechanism of action consists in an inhibition of central excitatory neurotransmitters, particularly glutamate. Both substances cause an improvement of subjective symptoms, sleep and, although to a lesser degree than dopamine agonists, PLMS. In contrast, over the long-term, $\alpha_2\delta$ ligands do not cause significant augmentation [44]. Side-effects include dizziness, somnolence, fatigue, headache and weight gain [44]. However, $\alpha_2\delta$ ligands are less effective in patients previously treated with dopamine agonists [45].

A small crossover study on eight elderly patients found that 300 mg gabapentin caused an increase in the apnoea–hypopnoea index [46]. In addition, pregabalin can cause significant respiratory depression in postoperative opium-induced analgesia [47].

Opioids such as oxycodone or methadone are widely used for the treatment of RLS resistant to dopamine agonists [36]. Although this class of drugs has been investigated in long-term studies [48, 49], few studies have investigated their effects on sleep disordered breathing. However, Walters *et al.* [50] performed polysomnography on seven out of 493 patients with RLS treated for an average of 7 years (range 1–15 years) with opioids as a monotherapy, and found a worsening of the respiratory disturbance index and minimum arterial oxygen saturation (S_{aO_2}) in two of them. Furthermore, a meta-analysis comprising seven studies with a total 803 long-term opioid users diagnosed with OSA found a small increase in the apnoea–hypopnoea index, but a moderate increase in the central sleep apnoea index [51].

Finally, benzodiazepines are frequently used for sleep stabilisation in RLS, although no convincing evidence exists of their therapeutic efficacy for the treatment of dysaesthesias or PLMS [36]. A meta-analysis involving five studies on a total of 233 patients with insomnia and chronic obstructive pulmonary disease (COPD) using benzodiazepines showed no significant increase (SD 0.15, 95% CI −0.25–0.56; p=0.46) in the percentage of time of S_{aO_2} <90% and mean S_{aO_2} in night sleep. However, in one study a mild increase in transcutaneous carbon dioxide tension (P_{CO_2}) during sleep was shown. Taken together, due to the possibility of increased maximum P_{CO_2} during sleep, caution is recommended in COPD patients with hypercapnia [52].

Benzodiazepines have been used for RLS; the most studied is clonazepam. They have been shown to decrease the number of arousals due to periodic limb movements [53]. A recent review by the Cochrane group showed that there is insufficient evidence to support or refute the use of benzodiazepines to treat symptoms of RLS [54].

Conclusions

OSA and RLS are two common sleep disorders that frequently coexist within the same patient. Although these disorders do not share a common pathophysiological mechanism, the presence of comorbidity with the other increases the severity of both disorders. Furthermore, comorbidity makes treatment of either of the two more difficult.

Treatment of RLS in the context of sleep disordered breathing should be started, whenever possible, with conservative measures. If not sufficient, a pharmacological approach should be started.

Dopamine agonists are a safe and effective treatment for RLS in OSA. However, their main complication is long-term augmentation of RLS symptoms. In contrast, $\alpha_2\delta$ ligands are effective and generally a safe treatment for RLS in sleep disordered breathing. However, these treatments are less effective in patients previously treated with dopamine agonists. Opioids are effective in patients refractory to dopaminergic

treatment, but, similarly to benzodiazepines, require caution regarding respiratory depression and central apnoeas. In addition, oral and intravenous iron treatments are generally safe and effective in the mid- to long-term.

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