

Restless legs syndrome: a new entity of neuropathic pain? Treatment with prolonged release oxycodone/naloxone combination

Franco Gemignani¹
Andrea Melpignano^{1,2}
Giulia Milioli^{1,2}
Silvia Riccardi^{1,2}
Liborio Parrino^{1,2}

¹Neurology Unit, Department of Neurosciences, University of Parma, Parma, Italy; ²Sleep Disorders Center, Department of Neurosciences, University of Parma, Parma, Italy

Abstract: Restless legs syndrome (RLS) is a disorder of sensorimotor integration characterized by an urge to move the legs when at rest, especially at night or in the evening, which is relieved by movement. Sensory symptoms may be prominent, often exhibiting features consistent with neuropathic pain. Iron deficiency and genetic factors are implicated in RLS causation in most patients. The pathogenetic model of impaired circadian dopaminergic modulation of sensorimotor integration circuitry at the spinal level is fitting with the co-occurrence of movement disorders, sensory symptoms, and sleep disruption in RLS. Accordingly, levodopa and dopamine agonists are effective for RLS symptoms, which compensate for the impaired descending control by diencephalo-spinal dopa(min)ergic pathway. Dopamine agonists are usually indicated as the first-line therapy, but their use in long-term treatment is often complicated by augmentation and impulse control disorder, thus alpha-2-delta ligands also are now considered the first line of treatment. It has been recognized that endogenous opioid system is also involved in the mechanisms generating RLS, possibly through an impaired modulation of pain pathways. Opioids can be considered as an alternative therapy, particularly in patients with augmentation and/or refractory to other treatments. Recently introduced prolonged-release oxycodone–naloxone was efficacious for short-term treatment of patients with severe RLS inadequately controlled with previous treatment. It will be important to assess whether opioids, as well as other drugs, are especially effective in definite RLS subtypes such as the painful phenotype.

Keywords: small fiber neuropathy, allodynia, hyperalgesia

Introduction: definition, main features, and diagnosis of restless legs syndrome

Restless legs syndrome (RLS) is a disorder characterized by an urge to move the legs when at rest, which is relieved by movement, with peak symptoms occurring at night or in the evening.¹ Restlessness is usually but not always associated with unpleasant sensations in the legs. These features have been incorporated in the RLS diagnostic criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG) in 2003,¹ and updated in 2012 with addition of a further criterion requiring consideration of differential diagnosis.²

RLS is quite common, as in European and American populations, about 2%–3% of adults suffer from clinically significant symptoms.³

The etiopathogenesis of RLS remains elusive, although the role of dopaminergic dysfunction, perturbation of iron homeostasis, and genetic factors is generally acknowledged.⁴ Recently, peripheral hypoxia in RLS, correlating with the severity of symptoms, has been described,⁵ and viewed as possibly involved in RLS pathophysiology,

Correspondence: Franco Gemignani
Neurology Unit, Department of Neurosciences, University of Parma, via Gramsci 14 I-43100 Parma, Italy
Tel +39 521 704 118
Fax +39 521 704 115
Email franco.gemignani@unipr.it



either as a primary trigger or a closely related secondary phenomenon.

Secondary forms of RLS are reported in association with various conditions, such as acquired iron deficiency, pregnancy, uremia, polyneuropathy.⁴

Several neural structures are potentially involved in RLS,⁶ but a central role has been attributed to the A11 diencephalo-spinal pathways, exerting a modulating control, and to spinal circuitry as a final common pathway directly related to motor and sensory RLS phenomenology.⁷ In particular, the involvement of dorsal horns of the spinal cord accounts for sensory symptoms and pain in RLS, which will be focused on in this review.

Sensory manifestations of RLS and pain

Although it is well known that abnormal sensations, characteristically indicated with a number of evocative terms, occur in association with RLS,¹ this aspect is little investigated, in comparison with sleep and movement disorders.

The questionnaire-based REST (Restless legs syndrome Epidemiology, Symptoms, and Treatment) population study³ rated an 88% prevalence of sensory symptoms (painful in 59.4%) in a cohort of 416 RLS “sufferers” (ie, with moderately or severely distressing RLS), more frequent than symptoms concerning sleep (75.5%) and movement disorders (37%). Sensory symptoms were most troublesome in 45.7% of patients versus 37.8% for disorders of sleep and 3.4% for symptoms affecting movement. Furthermore, a study involving 56 RLS patients, directly examined, along with 738 members of the French RLS Association (sent a postal questionnaire), showed that virtually all patients had sensory symptoms,⁸ challenging the existence of a pure motor form of RLS that was reported previously in approximately 10%–20% of subjects.¹

The prevalence of pain in RLS patients has been very differently rated, ranging from 17%⁹ to 80%.¹⁰ A prevalence of about 60% seems reasonable, according to some studies with more robust methodological procedures.^{3,8} It should be noted, however, that RLS typically presents as an intermittent condition. Karroum et al⁸ showed that many patients with painful RLS at onset merely reported uncomfortable sensations, and only subsequently complained of pain over the years, whereas other patients had painful RLS only occasionally, during periods of exacerbation of RLS symptoms. Accordingly, it has been estimated that up to 80% of patients with RLS report that the sensations are sometimes painful.¹⁰

As for descriptors of sensation associated with RLS, a recent study⁸ showed that “burning” was the most frequent sensory discriminator in patients with painful RLS (44% of clinically examined RLS patients, and 37% of a larger sample of the French RLS Association). It is perplexing that the descriptor “burning” was not mentioned at all in other studies.^{9,11}

A relationship between RLS and neuropathic pain has been suggested, considering the similarity of the words chosen by RLS patients with pain descriptors,^{8,12} however, this issue has not been specifically investigated using questionnaires recommended as screening tools for neuropathic pain, such as DN4 and ID-pain.¹³ Another argument indirectly favoring the view of RLS as a form of neuropathic pain is that RLS is quite frequent in patients with neuropathic pain due to polyneuropathy.¹⁴

Neuropathic pain has recently been redefined by the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP (International Association for the Study of Pain) as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”¹⁵ NeuPSIG diagnostic criteria require that pain distribution is neuroanatomically plausible and history suggests relevant lesion or disease, with confirmatory tests showing sensory signs confined to innervation territory of the lesioned nervous structure, and demonstrating lesion or disease explaining neuropathic pain.¹⁵ Pain associated with RLS can satisfy at least in part these criteria, considering that history and pain distribution are appropriate, and impairment of somatosensory pathways in RLS has been demonstrated by quantitative sensory testing.¹⁶ Further insight into possible mechanisms shared with neuropathic pain has been provided by the individuation in RLS of a peculiar somatosensory profile, characterized by profound hyperalgesia, without allodynia, in RLS patients.^{17–19} Hyperalgesia (increased sensitivity to pinprick stimuli) is a hallmark of central sensitization of dorsal horns to A-delta fiber nociceptor input, a mechanism operating in neuropathic pain.²⁰ It has been hypothesized that central sensitization in RLS is an aspect of increased spinal cord excitability related to impaired modulation by descending dopaminergic pathways.¹⁷

From mechanism(s) to treatment

The best data of clinical trials support the use of dopaminergics, alpha-2-delta ($\alpha 2\delta$) ligands, opioids, and iron, which are preferentially indicated in several RLS treatment guidelines.^{21,22} Other medications that have been reported to help RLS, but suffer from limited data, include benzodiazepines,

trazodone, baclofen, levetiracetam, carbamazepine, clonidine, and magnesium.

The serendipitous observation of dramatic RLS improvement with levodopa²³ originated the hypothesis of dopaminergic involvement in RLS^{24,25} and, on the other hand, supported the first-line use of dopamine agonists (ropinirole, pramipexol, rotigotine).^{21,22} It has been proposed that dysfunction of the dopaminergic system deregulates spinal structures generating complex limb movements constitutive of RLS phenomena, as well as of periodic limb movements while asleep. A likely responsible site has been individuated in the diencephalic A11 area,²⁶ close to the suprachiasmatic nucleus controlling circadian rhythms, which constitutes the major source of the spinal dopa(min)ergic projection into the dorsal horns,²⁷ interacting in turn with the flexion reflex circuitry. The dopaminergic model has been partly corrected by the demonstration that in nonhuman primates, the A11 neurons originating the diencephalo-spinal pathway are actually L-DOPAergic, whereas dopamine in the spinal cord presumably results from a local dopaminergic synthesis.²⁸

Long-term treatment with dopamine agonists and, above all, levodopa is complicated by augmentation, a paradoxical exacerbation and anticipation of RLS symptoms, made worse by higher doses of drugs.²⁹ This seems to be related to a dose-dependent dual action of levodopa on different subtypes of dopamine receptors with increasing doses. Levodopa and dopamine agonists at low doses induce D2-like activation, decreasing the excitability of the spinal cord, which is most probably responsible for the beneficial effect of dopaminergic treatment in RLS, whereas higher doses can overstimulate the D1-like receptors, which cause hyperexcitability of the spinal cord and are pronociceptive, resulting in augmentation.³⁰

It has long been observed that iron deficiency exacerbates RLS and iron replacement improves symptoms.³¹ Iron deficiency is related to, and possibly causative of the dopaminergic dysfunction, in that iron deficiency reduces dopamine-transporter function.³²

On the other hand, excitability of the spinal cord is strongly influenced by peripheral inputs participating in the system of flexor reflex afferents. The mechanism of $\alpha 2\delta$ ligands (gabapentin, gabapentin enacarbil, and pregabalin) has been attributed to binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, modulating the influx of calcium ions, and resulting in reduced neuronal network hyperexcitability.³³ This seems to occur at the level of presynaptic terminals, decreasing input to the dorsal horns,³⁴ which results in attenuation of neuropathic pain, as well as of the sensorimotor manifestations of RLS.

The opioidergic system is known to suppress the flexor reflex afferent pathways³⁵ and their ability to generate rhythmic spinal motor activity,³⁶ activating endogenous opiate receptors located on primary afferent sensory fibers.³⁷

This suggests that efficacy in RLS of therapeutic opioids mainly results from a spinal action, although the opioidergic system is also involved in sensory modulation at various neural levels.

In summary, it appears that dopamine agonists exert a direct action on the excitability of the spinal cord, whereas $\alpha 2\delta$ ligands and opioids act indirectly attenuating peripheral inputs, and this provides a rationale for combination therapy in refractory RLS patients, using drugs with action mechanisms operating at different sites.²²

Profile of prolonged-release oxycodone/naloxone in the treatment of RLS

Opioids now represent a potential therapeutic option for severe RLS and they are recommended as a second-line treatment, although with a low level of evidence,^{38–42} with only one randomized, double-blind study demonstrating that oxycodone was superior to placebo in improving RLS symptoms and polysomnographic findings.³⁸ Augmentation has not yet been reported for these medications, with the exception of tramadol, therefore opioids may also be considered in more severe cases of augmentation.⁴³ Common side effects of opioid administration include a very high incidence of nausea and constipation. Other concerns are sedation, an undefined potential for abuse in predisposed patients, and a possible risk for the development or worsening of sleep-disordered breathing and respiratory depression,⁴⁴ an important point as sleep apnea represents a not uncommon, insidiously developing comorbidity of RLS.⁴⁵

Coadministration of naloxone is able to prevent opioid-induced constipation through its local antagonistic action in the gut wall, while ensuring analgesia due to its low systemic bioavailability when taken orally.⁴⁶ A combination of prolonged-release (PR) oxycodone with PR naloxone (Targin, Targiniq, Targinact) is approved in many European countries for the treatment of severe to very severe RLS, after failure of dopaminergic therapy. The efficacy of oxycodone/naloxone PR (mean daily dose of oxycodone 22 mg and naloxone 11 mg) has been investigated in a 12-week, randomized, double-blind, placebo-controlled study (132 RLS patients assigned to PR oxycodone–naloxone vs 144 to placebo) with a 40-week open-label extension in

197 patients (RELOXYN study).⁴⁷ Patients enrolled had moderate-to-severe RLS symptoms, with mean initial IRLSSG score 31.6/40,⁴⁸ inadequately controlled by previous treatments. Oxycodone/naloxone PR was effective for short-term therapy of these patients, with a mean change from baseline of -16.5 (SD 11.3) in IRLSSG score (the primary endpoint), significantly greater when compared to the placebo group (-9.4 , SD 10.9). A beneficial effect seemed to continue through the open-label extension phase, suggesting also long-term efficacy. PR oxycodone–naloxone showed better results for some but not all secondary endpoints, such as those addressing subjective sleep quality and quality of life. There were high proportion of dropouts due to adverse events (15%) during the double-blind phase, however, high dropout is commonly observed in RLS studies, concerning even placebo groups.⁴⁹ A strength of this study was the accurate assessment, using a prospective stepwise approach, of a possible occurrence of augmentation, which was eventually excluded.

Overall, these findings confirm that opioids are a promising therapeutic option in severe refractory RLS, including patients with augmentation. The recommended starting dose of oxycodone/naloxone PR is 5/2.5 mg twice per day, which, according to clinical need, should be uptitrated at weekly intervals to a maximum of 60/30 mg/day, and gradually tapered-off, if no longer required, over a period of at least 1 week to reduce the risk of withdrawal symptoms. Notably, in the RELOXYN study, there were no reports of psychological dependence, opioid abuse/misuse, or tolerance throughout the study.⁴⁷

In the future, polysomnography studies are needed to investigate the effect of oxycodone/naloxone PR on sleep structure. As effect size of oxycodone/naloxone PR on the IRLSSG score was larger than that found in many previous studies with other drugs,⁴⁷ it would be important that long-term benefit is assessed in comparative studies of dopaminergic drugs. A further step to optimize indications of RLS management with opioids will be the individuation of potentially responder patients, possibly based on the characterization of specific RLS phenotypes. Given the clinical relevance of sensory symptoms, we think that the design of future trials should also include outcome measures mutated from pain medicine,¹³ as the sensory profile could represent a predictive factor, with regard especially, but not only, to opioid treatment. Patients with augmentation were initially excluded from the RELOXYN study, which did not provide direct evidence of effectiveness in established augmentation, while excluding its occurrence in the course of oxycodone/naloxone PR

treatment.⁴⁷ The utility of therapy with oxycodone/naloxone PR deserves to be specifically assessed in RLS patients experiencing augmentation, also considering that opioids suppress the long-latency flexor reflex afferent pathways,³⁵ whereas facilitation of the same pathways is considered a possible substrate of augmentation.⁵⁰

There is no information concerning the potential effectiveness of oxycodone/naloxone combination in patients with secondary RLS. In this regard, patients with RLS secondary to polyneuropathy could be of interest, as this subgroup is especially afflicted by painful symptoms.¹⁴

Disclosure

The authors report no conflicts of interest in this work.

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