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FIBROMYALGIA (M PERES, SECTION EDITOR)

# Restless Legs Syndrome and Pain Disorders: What's in common?

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**Abstract** Between 10 % and 30 % of the population report chronic pain. More than half of these also have sleep complaints. From considering these data, it can be inferred there is a significant overlapping between these conditions. Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED) is characterized by complaints of an "urge to move" frequently associated with dysesthesias. From that perspective, these sensations can also have painful characteristics. By the same token, the presence of comorbid diseases as predicted by a higher prevalence RLS/WED, have many of them with pain as an important complaint. Pain is a multidimensional response involving several levels of expression ranging from somatosensory to emotional. The potential shared mechanisms between RLS/WED and pain may involve sleep deprivation/fragmentation effect, inducing an increase in markers of inflammation and reduction in pain thresholds. These are modulated by several different settings of neurotransmitters with a huge participation of monoaminergic dysfunctional circuits. A thorough comprehension of these mechanisms is of utmost importance for the correct approach and treatment choices.

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## Introduction

Between 10 % and 30 % of the general population report chronic pain. More than half of these (44-89 %) [1, 2] also have sleep complaints. Considering only musculoskeletal pain and fibromyalgia, the prevalence of sleep complaints reaches 99 % [3]. Conversely, approximately 50 % of those complaining of poor sleep suffer from chronic pain [4]. There is a multifactor comorbid relationship between these two conditions, in which a variety of interactions is expected, such as one condition increasing the risk of another, worsening the outcome or impact in life quality, or even just interfering with each other's treatment.

Many mechanisms could explain the sleep-pain interrelationship. Sleep deprivation or fragmentation decreases the threshold and the tolerance to pain similar to other stimuli such as light and noise [5, 6]. Also, it is not uncommon that sleeping longer than average increases pain for the next day [5]. Conversely, painful conditions enhance or cause a cortical hyperalert state, which compromises sleep architecture. It also causes or triggers sleep disturbance [7].

It is well-known in the clinical field, and endorsed by recent scientific evidence that, poor quality sleep worsens pain intensity and frequency, which also impacts on the quality of life and the therapeutic efficacy on pain disorders [8, 9]. Besides, chronic pain may be a perpetuating factor for poor sleep [1]. Among sleep disorders leading to sleep deprivation

or fragmentation restless legs syndrome (RLS) and periodic limb movement of sleep (PLMS), there are key conditions. Both can be primary/idiopathic, secondary to another disorder, and comorbid. We review in this paper the specific interactions between primary and comorbid RLS, PLM, and pain.

## Restless Legs Syndrome/Willis-Ekbom Disease: Sensory, Motor, or Pain Disorder?

RLS or Willis-Ekbom disease (WED) is a common neurological sensorimotor disorder with a substantial negative impact on sleep, quality of life, and general health [10]. The prevalence of RLS/WED symptoms is about 2.4-10 % in western countries [11, 12•, 13••, 14•] and less frequent in East Asia and sub-Saharian Africa [15–17]. In a survey enrolling more than 16,000 adults, Allen et al., found that despite 81 % of the patients having reported their complaints to the primary care physician, only 6 % were given a precise diagnosis of RLS/WED [18].

The essential feature of RLS/WED is the "urge to move" associated with discomfort. Most patients with RLS/WED complain of dysesthesia with unpleasant or uncomfortable sensations predominantly in the legs, coming from deep within the legs and spreading over large areas of the thighs, calves, or both (see Table 1 for diagnostic criteria). Despite been named restless legs, symptoms may occur, albeit rarely, in the arms or other regions. The urge to move and the unpleasant sensations are worse in the evening or at night and are relieved by movement [13••]. These features may reflect an increased sleepiness in the evening compared to the daytime, decreasing of motor activity in the evening, and a circadian pattern for RLS/WED manifestations. These are significantly correlated to the decrease in core body temperature, subjective vigilance, and increasing salivary melatonin secretion [12•, 19•].

The terms chosen by the patients to describe their sensations are extremely variable: electrical (43 %), prickling (30 %), burning (29 %), tingling (27 %), heaviness (7 %), pressure (7 %), tenseness (7 %), tugging (7 %), and others. Up to 61 % of RLS/WED patients report painful sensations. The painful RLS/WED subgroup tends to describe a more frequent involvement of the upper limbs [20•, 21]. The relationship between the sensory (unpleasant sensation/urge to move) and motor components (movement) in RLS/WED remains unclear.

Besides the urge to move, which could be understood as a restricted akathisia, another of the signs of motor dysfunction in RLS/WED is the periodic leg movements (PLM). Originally called "nocturnal myoclonus" it typically consists of rhythmic extension of the hallux, together with dorsiflexion of the ankle and flexion of knee and hip. These are very common manifestations in RLS/WED patients, occurring in up to 90 % of them [22], and, in about 8 % of the general population, incidence increases with age [23]. Although quite specific for RLS/WED, they are not very sensitive since they occur in many other conditions (OSAS, REM Sleep Behavior Disorder, Narcolepsy, Bruxism, antidepressants) and also in an idiopathic form as well [24, 25••, 26]. The prevalence of PLMS (>15/hour) in adults is about 8 % [23] but it occurs in 45 % of the elderly.

Periodic leg movements may be seen in sleep (PLMS) or wakefulness (PLMW). PLMW may happen during quiet rest or yet in wakefulness episodes during the period of sleep. Its clinical significance, if it exists, is on delaying sleep onset or even the return to sleep and fragmenting it. Often, although the PLM is evidenced by a polysomnogram, there are no symptoms [27]. The amount of PLMS, but not PLMW, during the sleep period relates to RLS/WED severity [28]. Contrary to expectations, PLMS are not directly related to the primary RLS/WED morbidity [28], rather they may reflect some RLS/WED independent mechanism. When PLMS is associated with clinical sleep disturbance or fatigue that cannot be accounted for by another sleep disorder or other etiology, then

**Table 1** Diagnostic of RLS/WED [13••]

| |
|---|
| RLS/WED five essential diagnostic criteria (all must be met) |
| (1) 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. |
| (2) 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. |
| (3) 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. |
| (4) 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. |
| (5) The occurrences of the above features are not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, and habitual foot tapping). |
| RLS/WED specifiers for clinical course |
| (A) Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year. |
| (B) Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events. |
| RLS/WED specifier for clinical significance |
| The symptoms of RLS/WED/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, and cognition or mood. |
| Common differential diagnosis are: polyneuropathy, leg cramps, lymphatic diseases, leg cramps, positional discomfort, myalgia, leg edema, radiculopathy, habitual foot tapping, symptomatic venous insufficiency, peripheral artery disease, eczema, orthopedic conditions, painful legs and moving toes, and anxiety. |

it can be established the diagnosis of Periodic Limb Movement Disorder (PLMD) (Table 2).

Two prospective cohort studies involving, together, more then 5,000 patients and lasting, respectively, 2.1 and 5 years, evaluated the effect of the presence of chronic comorbid conditions (diabetes, hypertension, myocardial infarction, obesity, stroke, cancer, renal disease, anemia, depression, thyroid disease, and migraine) on the risk of RLS/WED/WED. The results showed that an increase in the number of comorbid diseases predicted higher prevalence and incidence of RLS/WED/WED [29]. Therefore, RLS/WED/WED is an intriguing phenomenon, involving many local and systemic aspects that can be clinically understood as a sensorial dysfunction by the common descriptors that always converge to unpleasant/uncomfortable sensations. It also can be seen as a sensorimotor disorder since it is primary for the diagnosis, at least, that there is the intention to move, not to mention the strict association with PLM. However, considering patients perception… yes, we dare to say that, it also can be seen as a pain disorder.

## PAIN

Pain is an organic response involving systemic cellular mechanisms such as gene expression and modulation of receptors resulting in behavioral reaction related to the activation of brain regions associated with emotional, instinctive (limbic structures), planning behavior (frontal cortex, supplemental motor area) and also regions implicated with attention, decision making, working memory, and body recognition (frontal and temporal gyri, inferior parietal lobule, precuneus, lingual cortices) [30, 31].

Pain generally starts with the activation, above a specific threshold, of peripheral nociceptors and mechanoreceptors in response to stimuli impact, pressure, temperature, and others.

**Table 2** Diagnostic of PLMD

| Criteria A-D must be met |
|---|
| A. Polysomnography demonstrates PLMS, as defined in the latest version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events. |
| B. The frequency is>5/hour in children or>15/hour in adults. |
| C. The PLMS cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning. |
| D. The PLMS and the symptoms are not better explained by another current sleep disorder, medical or neurological disorder, or mental disorder (e.g., PLMS occurring with apneas or hypopneas should not be scored). |

American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014

The first painful stimulus travels from high threshold receptors via A-δ (myelinated) fibers to the CNS (Central Nervous System) providing acute qualitative and location information. The somewhat delayed, diffuse, dull or burning ("second') type of pain is transmitted by C fibers (unmyelinated) and results in more persistent sensations [32]. A crucial phenomenon involved in the origin of complex painful contexts is the sensitization process, in which pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli. Instead, central sensitization produces distortions in the experience of pain's duration, intensity, and even location by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations. It may be mediated by upregulation (neuropeptide Y) and sprouting of terminals in the spinal cord with subsequent stimulation of ascending central pain pathways. Furthermore, central sensitization is associated with glutamate acting at N-metyl-D-aspartate (NMDA) receptors [33].

Pain stimuli are associated with multiple and complex activations in the brain and not only to circuits specifically pain-related. Using functional magnetic resonance imaging (f-MRI) in a delayed discrimination paradigm, Lotsch et al., studied brain activations related to subjects' comparison of different pain intensities. The results suggested that, brain activations related to the second stimulus (to be compared with the first one), were significantly greater than with the first stimulus. Besides that, the "comparing pain" brain activation regions included sites, other than the "pain matrix" (regions commonly activated during the pain experience), such as the aforementioned ones associated with attention, decision-making, working memory, and body recognition [31]. These findings endorse the hypothesis that comparing pain, as automatic behavior in frequent pain sufferers, involves short-term memorizing and attention among other complex integrative central functions. Thus, pain may act as a biological alerting system that gains the subject's attention and then dominates most other perceptions and activities involving pain-specific and, importantly, non-pain-specific brain regions. The longer it occurs and, with frequent pain taking place, then different levels of changes in those networks may occur associated with neuronal plasticity and/or supportive cells modifications resulting in a different types of modulation. This modulation is probably found in the context of chronic pain and functional diseases. Therefore, the perception itself, tolerance and the emotional response to pain, are also associated to this "central modulation" along with gene expression and a particular environment (e.g., proteins acting at any point of the pain process like the periphery, the spinal cord or central nervous system) [34, 35]. Accordingly, subjective perception of pain may sometimes arise from a normally painless stimulus. From nerve endings activation to the final reactive behavior to pain, there is a multifactor chain of interactions, starting with the

stimulus (noxious or not) and going through pain perception by which a wide variety of behaviors can be expected.

## RLS/WED and Pain

The disagreeable and hallmark sensory symptom, described in many ways by RLS/WED patients, has been reported as painful by about one half of RLS/WED patients [20], but isolated pain without an urge to move does not constitute RLS/WED [13••]. Also, the significant correlation of specific questionnaires, one to evaluate RLS/WED symptoms severity (The International Restless Legs Syndrome Study Group RLS/WED severity scale [36]) and two other pain scales (Pain Rating Index, and number of words chosen derived from the McGill Pain Questionnaire) suggest painful characteristics among RLS/WED sensory symptoms [37••].

To investigate the possibility of a peripheral neuropathy underlying RLS/WED pathogenesis, Polydefkis et al. [38], using skin biopsies of 22 RLS/WED patients, found a prevalence of small sensory fiber loss (SSFL) neuropathy in 36 %. In brief, those authors conclude that two forms of RLS/WED exist: one is triggered by painful dysesthesias associated with SSFL, has later onset, and no family history; and one without involvement of SSF, with an earlier onset age, positive family history for RLS/WED, and no pain.

Stiasny-Koster et al., showed reversible alterations in somatosensory and, specifically, pain mechanisms among RLS/WED patients. Comparing 40 untreated, primary RLS/WED patients with 40 age-matched and gender-matched healthy volunteers, the authors identified static hyperalgesia to punctate stimuli (the sensory pathway involved in withdrawal reflexes), reduced tactile sensitivity, and paradoxical heat sensation in the RLS/WED group. Long term (2-20 months) treatment with levodopa normalized the changes mentioned above (compared to control group) [37].

The reduction of hyperalgesia in RLS/WED patients by long-term dopaminergic treatment together with normal electrophysiology and reflexes, suggests that the tactile deficit in (idiopathic/primary) RLS/WED would be solely functional. Moreover, the pathophysiology of RLS/WED would include disturbed supraspinal pain modulation involving the basal ganglia and/or descending dopaminergic pathways [39]. Recent fMRI data, comparing thalamic connectivity of 25 drug-free RLS/WED patients with 25 controls, showed, in the RLS/WED group, reduced thalamic connectivity with the right parahippocampal gyrus, right precuneus, right precentral gyrus, and bilateral lingual gyri; however, the right superior temporal gyrus, bilateral middle temporal gyrus, and right medial frontal gyrus showed enhanced connectivity with the thalamus. Symptoms severity was negatively correlated with connectivity between the thalamus and the right parahippocampal gyrus [40•]. This suggests deficits in controlling and managing sensory information, supporting the hypothesis of RLS/WED as a dysfunction of somatosensory processing.

Traditional but, still speculative, data support the assumption that an important center for these supraspinal dopaminergic sensitive modulatory systems would be the A11 region (dorsal-posterior hypothalamus). This small dopaminergic nucleus exhibits local hypothalamic connections, projections to the neocortex, the serotonergic dorsal raphe, and they descend as the sole source of spinal dopamine mainly through the dorsolateral funiculus and the intermediolateral nucleus, which are the origin of sympathetic preganglionic pathways [41]. The consequences of the loss of A11 dopaminergic inhibitory influences would be: hyperactivity in the A-δ pathway and in the protective reflexes; increase in the sympathetic drive (direct action via intermediolateral nucleus and/or via release of excitatory serotoninergic influence coming from the dorsal raphe); dysfunctional activation of high threshold muscle afferent (focal akathisia); dysfunctional activation of high threshold muscle afferents and their control by movement (focal akathisia) - this transmission can be blocked by low threshold muscle afferents coming from proprioceptors activated by movement; and cortical sensory processing of akathisia experience.

In the authors' own clinical experience, psychological mechanisms associated with a dysfunctional control of attention, seen in certain personality traits and/or psychiatric disorders, is of fundamental importance to the magnitude and repercussion of RLS/WED symptoms and, therefore, to the final result of the binomial RLS/WED - pain. Increased attention to bodily sensations, sensitivity to pain, often followed by catastrophizing, negative, pessimistic thoughts, play important role in illness behavior, mainly in functional diseases where central facilitation mechanisms are crucial.

In addition to all the potential shared mechanisms, RLS/WED and PLMD may, just by their sleep deprivation/fragmentation effect, induce an increase in markers of inflammation and reduction in pain thresholds to possibly precipitating or worsening pain disorders [6, 42•].

### RLS/WED and Fibromyalgia

A recent study, enrolling 3,060 respondents for a questionnaire on pain and RLS/WED, showed a prevalence of RLS/WED in chronic multisite pain as high as 55 % (increasing with the number of pain sites and severity) [43•]. About 33 % of FMS patients met RLS/WED diagnostic criteria in a study using validated questionnaires for RLS/WED and the 1990 American College of Rheumatology guidelines criteria for fibromyalgia (FMS) [44]. Recent work from Franca et al., studied 194 fibromyalgia patients, showed a prevalence of RLS/WED among FMS of 23.4 % [45]. Civelek et al., described RLS/WED in 42.6 % of 115 subjects in a FMS group.

Compared with FMS alone, the coexistence of RLS/WED - FMS led to higher rates of sleep complaints, daytime sleepiness, and impairments in the quality of life as measured, respectively, by the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Fibromyalgia Impact Questionnaire (FIQ) [46].

Stehlik et al., studying FMS and multisite pain patients with RLS/WED, have proposed some insights on common causal pathways [43•]. According to those authors, there is a dysregulation of the dopaminergic circuitry, with a reduced expression of D2 receptors (anti-nociceptive) and loss of pain modulation. This reduced dopaminergic transmission could, in fact, be responsible for several other dysfunctions as a reduced binding of μ-opioids in the nucleus accumbens, which has been correlated with the affective pain. SPECT studies have shown a reduced dopaminergic transmission in FMS [47], and a dopaminergic treatment significantly reduced pain rates in another study [39]. Furthermore, the beneficial analgesic effects of N-Methyl-D-Aspartate receptor agonists in FMS have been attributed to their D2-receptor agonistic properties [48]. Another important factor to consider is brain iron levels, which have been found to be decreased in many RLS/WED patients, mostly women. Iron is an essential co-factor for the enzyme tyrosine hydroxylase, responsible for regulation of dopamine synthesis. Ortancil et al., have shown reduced ferritin levels in fibromyalgia and this has been considered a major link for the association of RLS/WED and multisite chronic pain conditions [49]. Furthermore, chronic pain implies a perpetual activation of the hypothalamic-pituitary-adrenal axis, leading to increased adrenaline and noradrenaline levels, which are synthesized from dopamine. Thus, the association of a reduced dopaminergic synthesis to an increased utilization could be responsible for the dopaminergic transmission deficiency, itself leading to lack of pain modulation and RLS/WED symptoms. The transformation of normal sensory inputs to pain sensation due to some peripheral nervous system dysfunction, and alterations in central somatosensory processing [50] is another commonly proposed mechanism between multisite pain conditions and RLS/WED.

## RLS/WED and Migraine

Most estimates of RLS/WED prevalence among migraine patients is higher than in the general population, reaching 25 % [51–53]. Severity and family history for RLS/WED are also higher in migraine then in non-migraine patients [51–54]. In two large cross-sectional studies involving, respectively, 31,370 female and 22,926 male participants, any history of migraine was associated with a multivariable-adjusted OR of 1.22 and 1.20 [55, 56]. Migraine aura status did not impact the odds for having RLS/WED. The risk for RLS/WED in migraine patients is similar for women and men [55, 56].

Dopamine has, traditionally, been considered as playing a role in the pathogenesis of migraine. There are various non-specific dopamine D(2) receptor antagonists that show good clinical efficacy in migraine, and also a number of polymorphisms of dopaminergic genes related to migraine [57]. Blocking dopamine receptors with some anti-migraine medications, or other dopaminergic drugs used to treat chronic headache increases the likelihood of development of drug-induced akathisia in patients with RLS/WED compared to those without RLS/WED [58]. Some migraine sufferers are hypersensitive to dopamine agonists, at risk for some symptoms such as yawning, nausea, drowsiness, mood changes, and food cravings [57]. Still, a recent paper reported treatment of ten RLS/WED plus migraine patients with pramipexole with 50 % improvement of migraine and 80 % of improvement in morning headache [59]. These data have to be weighted considering the distress caused by the symptoms of the sleep disorder in migraine versus direct harm of its use in migraine. No matter the mechanisms by which dopaminergic drug controlled the pain, this study stresses the importance of controlling comorbid conditions.

By using fMRI to access brain response to painful heat in migraneurs and healthy volunteers, Scwedt et al., demonstrated that migraneurs may have a greater pain-induced activation of brain regions involved in pain perception and pain memory [60]. Cognitive pain as processed pain may reflect a greater cerebral sensitivity related to hypervigilance for pain. Another clue linking the pathophysiology of migraine and other functional/dopamine diseases would be the evidence of iron (fundamental for dopamine synthesis) alterations. One small MRI study correlated, in young migraine patients, increased iron accumulation in the putamen, caudate, and red nucleus with the frequency of the attacks and the length of disease's history [61]. Other motor or sensorimotor disorders involving dopaminergic (extrapyramidal) alterations have also been linked to migraine, such as Tourette's syndrome, Parkinson's disease, dystonia, and essential tremor [51].

Hence, as in RLS/WED, dysfunctional interactions between the dopaminergic modulation center (A11) and the serotoninergic regional (raphe, periaqueductal grey matter) networks may, in predisposed individuals, contribute to migraine.

## RLS/WED and Polyneuropathy (PN)

The differential diagnosis of polyneuropathy also can be confusing since the subjective description of the symptoms of polyneuropathy may be similar to the description of the symptoms of RLS/WED. In addition, the patient's description of RLS/WED symptoms may also resemble the complaints of polyneuropathy. This context was illustrated by a recent study

in comparing the prevalence of RLS/WED between patients with diabetic peripheral neuropathy (DPN) ($N$=199) and patients with osteoarthritis leg pains (OA) ($N$=220)[62]. Using RLS/WED diagnostic criteria from the international classification of sleep disorders 2nd edition (ICSD-2), the authors found a higher prevalence of RLS/WED in the DPN group comparing with the OA (22 % X 3.6 %) [62]. However, when diagnosis was confirmed, or rejected, through a validated structured diagnostic interview and face-to-face interviews by two neurologists, only 8 % of the DPN group had RLS/WED [62].

Among patients with type 2 DM, nearly all patients with RLS/WED have DPN. RLS/WED was more common in patients with painful peripheral neuropathy than non-painful neuropathy [63]. Perhaps the involvement of A and C fibers in diabetes have a sum effect to the central mechanisms underlying, triggering or worsening, the RLS/WED symptoms.

### RLS/WED and Somatoform Pain Disorder

Accordingly, Aigner et al., found there is a 42 % prevalence of RLS/WED in somatoform pain patients. The association of RLS/WED and somatoform pain may be partially explained by a few mechanisms related to an unbalance in the monoaminergic system [64]. Hypothamus-pituitary-adrenal axis hyperactivation seen in chronic pain may despoil dopaminergic system. If there is an individual organic trend (dopaminergic failure susceptibility) towards developing RLS/WED than, it can be triggered or worsened.

Besides, medication overuse by a chronic pain disorders population, can contribute to RLS/WED development.

## Neurochemistry/Neurotransmitters

### Opioid/Dopamine

Most mechanisms implicated in the pathogenesis of RLS/WED involve endogenous opioid, dopamine, and iron systems. Sun YJ et al., demonstrated that the apoptosis of dopaminergic cells in the substancia nigra induced by iron chelation and could be prevented by the administration of a peptide opioid [65]. Eventually, endogenous opioid system integrity or opioid treatment may protect the dopamine system. Also, the exuberant and reliable therapeutic response to opioid and dopaminergic agonists supports the hypothesis of the key involvement of opioids and dopamine networks in the pathophysiology of RLS/WED and PLMS [66]. The opioid mechanism probably works on a dopaminergic substrate as illustrated by Montplasir, with an RLS/WED case in which codeine alone improved RLS/WED and PLMS. In the same patient, the association of pimozide (dopaminergic antagonist) partially reversed the symptoms [22]. On the other side, naloxone (opioid antagonist) did not reduce the efficacy of bromocriptine (dopamine receptor agonist), suggesting that the effect of dopaminergic drugs on RLS/WED - PLMS is not mediated through opioid action. Besides that, neither opioid nor dopamine antagonist triggered or worsened RLS/WED - PLMS symptoms in drug-free idiopathic RLS/WED patients [67].

### Serotonin (5-HT)

Using cerebral SPECT and the International RLS/WED Study Group (IRLSSG) Severity Scale to study 16 drug-naive RLS/WED patients, Jhoo et al,, found that the availability of serotonin transporter in the pons and medulla was decreased as the severity of RLS/WED syndrome increased. That means, RLS/WED symptoms may be exacerbated by the increase in the brainstem in serotoninergic tonus [68].

Serotoninergic transmission has long been implicated in a variety of pain disorders including migraine, temporomandibular pain, and pain conditions mediated by the trigeminal system [69]. Serotonin transporter (5-HTT) is a key regulator of 5-HT in a neurological system. 5-HTTLPR gene polymorphism influences the analgesic response to the opioids and pain modulation at the supraspinal level. It is related to the susceptibility to trigeminal neuralgia and to its severity [34]. Moreover, there's a condition-specific effect of central serotoninergic modulation of pain that impacts pain experience. While in one study, no relationship was shown between 5-HTTLPR polymorphism and pain perception in fibromyalgia patients and healthy controls, a few argued an important impact of the short allele of 5-HTTLPR in the emotional modulation of pain and even an association of the short-short genotype to the increased risk for trigeminal neuralgia [34].

### Glutamate

Recent work by Allen et al., revealed increased glutamatergic thalamic activity in RLS/WED. Besides confirming a new RLS/WED abnormality in a major non-dopaminergic neurologic system, the thalamic involvement points toward a candidate mechanism explaining the disturbed arousal system leading to sleep disruption in RLS/WED independent of PLMS. Higher levels of glutamatergic activity positively correlated with primary measures of sleep disruption such as wake after sleep onset (WASO, sleep latency and total sleep time) and negatively correlated to total sleep time subjectively estimated [70•]. This was the first data to demonstrate a relation between a neurotransmitter system and RLS/WED related sleep disruption. Also, chronic musculoskeletal pain has long been related to increased glutamate in many levels of pain [71].

### Iron

Iron takes part in many levels of the sensorimotor processing and in dopamine and serotonin availability [72]. Thus, iron supports RLS/WED and also pain mechanisms. There is evidence for iron modulation of acute and chronic pain at the spinal cord level in rodents [73]. This finding could explain the aforementioned reversible functional changes in A-δ and C-fibers in RLS/WED patients [37]. A few studies, in animals, correlated a decrease in brain iron with high glutamate levels in many regions, mostly in the ventral midbrain and striatum [33]. Besides, low ferritin levels in FMS (compared with controls and even with the normal range) may have a role in the fibromyalgia etiology [49].

### Gamma-Aminobutyric Acid (GABA)

In a recent study, using proton magnetic resonance spectroscopy, Winkelman et al., found that both symptom severity and PLM in RLS/WED were related to elevation of GABA levels in the thalamus and a reduction in cerebellum [74•]. It is matter of speculation if the GABA inhibitory activity in the thalamus would blunt normal sensitive modulation, thus, resulting in RLS/WED symptoms and PLM. Besides that, cerebellar overactivity, due to loss of inhibitory GABA influence, could contribute to RLS/WED via striatum. Conversely, successful treatment of RLS/WED, PLMS, PLMD [75], and a pain affective component with benzodiazepines, supports a widespread gabaergic inhibitory action.

Within the pain conditions, GABA takes part in descending supraespinal nociception control and also in the mechanisms of central sensitization [76].

### Vitamin D

The role of vitamin D in RLS/WED and also a few pain disorders has been studied. It has been shown that low doses of 1 alpha, 25 dihydroxyvitamin D3 protect the dopaminergic neurons against toxins that cause a decrease in glutathione content [77]. Decreased glutathione content has been shown to cause selective dopaminergic neuron death [78]. A recent study found vitamin D deficiency to be significantly associated with RLS/WED in patients with unspecific musculoskeletal complaints [79]. Furthermore, Von Kanel et al., evaluated 174 patients with chronic pain and found 71 % of them had a vitamin D deficiency (25-OH vitamin D<50 nmol/L). Lower 25-OH vitamin D levels were related to greater pain severity [80]. In a small prospective controlled essay in pediatric patients, vitamin D supplementation (with previous insufficiency, deficiency, or even normal serum levels) in addiction to amitriptyline, reduced the number of migraine attacks [81]. Recent treatment trials involving chronic pain patients, mostly FMS, have shown that deficient, or insufficient, levels of 25-OH vitamin D3, correlates with greater pain intensity and worse scores in quality of life questionnaires. Supplementation with vitamin D decreases pain intensity [80, 82]. Similarly, Oran et al. [79] compared the prevalence of RLS/WED in patients with low and normal levels of vitamin D finding a significant correlation between vitamin D insufficiency and the presence of RLS/WED. Data regarding vitamin D and migraine are inconclusive [83, 84]. In short, correction of vitamin D levels seems to be an important part of the RLS/WED and pain conditions in those patients with deficient or insufficient levels.

### Melatonin (MLT)

The circadian variance is one of the RLS/WED hallmarks. Some studies suggest that melatonin could increase an evening's RLS/WED symptoms and PLM [85] and, that bright light melatonin suppressing effects could be implicated in the amelioration of discomfort sensations [86]. Hence, melatonin could lead to a depressed dopaminergic activity in the CNS, where melatonin and dopamine play a reciprocal inhibitory role. Impaired dopaminergic influences on sensory and motors inputs would increase the likelihood of RLS/WED and possibly spinal cord generated PLM [86]. Conversely, in PLMD patients, without RLS/WED, exogenous melatonin may improve PLM index and arousals [87] endorsing the aforementioned hypotheses of different mechanisms surrounding PLMD and PLMS within RLS/WED [25]. Experimental and clinical evidence have indicated that MLT possesses analgesic properties, mostly related to MT1/MT2 receptors interaction, acting via activation of opioid receptors, GABA-ergic transmission, and ion channels [88, 89]. In rodents, MLT (MT1 and MT2) receptors have been identified in cerebral structures related with pain, such as the thalamus, hypothalamus, trigeminal tract, trigeminal nucleus, and pituitary gland [90]. Moreover, they have been found in the spinal cords of chickens and rabbits [91].

## Circadian Pattern

As RLS/WED symptoms, pain intensity in several chronic pain conditions, including painful diabetic neuropathy, postherpetic neuralgia, and phantom limb pain, are most pronounced in the evening and at night [92–94]. For instance, 52 % of patients with painful diabetic neuropathy reported that pain was worse at night, whereas only 17 % had worse pain in the morning [95]. To what extent this is related to an endogenous circadian rhythm, as with RLS/WED [96], vs other confounding features (e.g., time awake, environment, and distraction) is uncertain. This is because specific studies have not been performed in these pain conditions. Movement

usually results in partial relief of symptoms in patients with RLS/WED, but it does not significantly improve pain in chronic neuropathic pain conditions.

## Treatment Implications

Treating pain and RLS/WED demands understanding the pathophysiology of the mechanisms underlying the symptoms, besides caution with drugs effects since, frequently, treating one condition may worsen the other. Further, the diagnostics must be precise, always watching for any additional comorbidities, since both RLS/WED and chronic pain increase the risk for other diseases. Treating sleep disorders may not solve pain, and treating pain could not fix a sleep disorder. In the case of comorbid incidence of those disorders, it is mandatory to have a dual therapeutic approach.

RLS/WED and PLM treatment may be pharmacological and non-pharmacological. First-line pharmacological approaches for RLS/WED are the dopaminergic agonists (the most used are pramipexole and ropinirole), and the α-2-δ ligand (gabapentin enacarbil, gabapentin, and pregabalin). Second- line treatment are the opioids, generally in lower doses than that used for pain control. There is some evidence towards benzodiazepines (clonazepam) [97•].

The mechanism of action of the α-2-δ ligand in neuropathic pain, binding to voltage-gated calcium channels at the dorsal horn of the spinal cord, reducing excitatory neurotransmitter release (e.g., substance P and glutamate) and/or modulating descending inhibition, is also effective in RLS/WED [98••].

In the authors' experience, even with normal ferritin levels, in most RLS/WED cases, it is worthwhile to have iron supplementation. This applies especially in cases of RLS/WED in the context of consumptive conditions such as cancer or other systemic diseases.

Several substances or medications exacerbate or can even engender RLS/WED or PLMS. Many of them are often used in pain treatment. These include tricyclic or other antidepressants (such as serotonin reuptake inhibitors), dopamine ($D_2$) antagonists, antihistamines, caffeine, and alcohol [99].

A mild RLS/WED worsened by a pain condition will not go away just by treating pain. A chronic pain condition, even thought triggered or worsened by sleep deprivation and/or distress associated to RLS/WED - PLM, will not be solved by treating only the sleep condition. In such cases, comorbidities must be individually approached at the same time.

## Conclusion

Based on the common pathophysiology, frequent clinical overlapping and a comorbid relationship are expected between chronic pain and RLS/WED. However, interrelation goes beyond a few common pathophysiological pathways. Within both conditions, different kinds of stimuli (peripheral or central) of a different nature such as inflammation, changes in nerve environment or distress-related can result in an unpleasant experience.

Considering that the pain sensation may become decoupled from primary noxious stimuli, similar central mechanisms of sensitization could also explain the variety of central RLS/WED complaints as well as its complications such as augmentation. The description of RLS/WED complaints is subjective in two ways: the way patients perceive it, and also the way they describe it. Since perception is related to subjects' profile of pain circuits, psych structure, and comorbidities, the ability for description is also related to education, language, and previous experience. A typical pain report, in RLS/WED suspects, demands further investigation for other peripheral and/or systemic disorders (vascular, diabetes, polyneuropathy and others).

Thus, the most broad and relevant association is based on the clinical aspects. It is of primary relevance that the early recognition of this comorbid relationship be made in order to support a better outcome, no matter what was the primary condition.

### Compliance with Ethics Guidelines

**Conflict of Interest** Dr. Leonardo Ierardi Goulart and Dr. Raimundo Nonato Delgado Rodrigues each declare no potential conflicts of interest.

Dr. Mario Fernando Prieto Peres is a section editor for *Current Pain and Headache Reports*.

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- •• Of major importance

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