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Circadian Pattern in Restless Legs Syndrome: Implications for Treatment Posology

Celia Garcia-Malo[1] Irene Cano-Pumarega[1,2,3] Andrea Castro-Villacañas-Farzamnia[1] Sara Boi[1]

[1] Neurology Department, Centro Integral de Sueño y Neurociencias (CISNe), Madrid, Spain
[2] Respiratory Department, Sleep Unit, Hospital Ramón y Cajal (IRYCIS), Madrid, Spain
[3] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain

Address for correspondence Celia Garcia-Malo (e-mail: celia.garcia.malo@gmail.com).

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Abstract

The symptoms of restless legs syndrome (RLS) follow a circadian pattern, as inducated in the current RLS diagnostic criteria. Indeed, subjects with mild-to-moderate RLS suffer or not from RLS symptoms depending on the time of day, resembling an above-threshold state periodically followed by a below-threshold state. Although the circadian clock is crucial in the clinical features of RLS, research assessing the ultimate drivers of circadian rhythmicity is still very limited. In the present review, we show current evidence on circadian variations of neurotransmitters involved in the pathophysiology of RLS (systemic iron metabolism, brain iron homeostasis, adenosine, dopamine, glutamate, and endogenous opioids). Secondly, an overview of available therapies for RLS is presented, including information on current recommendations for symptomatic treatments in RLS.

We discuss the importance of further research into the circadian oscillations that occur in RLS, so that they can be managed, and a protective below-threshold state can be established on an individualized basis. In addition, we also discuss the current dosing of the medications prescribed in RLS symptomatic treatments, and how circadian factors should be considered to better adjust dosing on an individualized basis and increase the therapeutic benefit.

Keywords

- restless legs syndrome
- circadian pattern
- RLS symptoms
- RLS symptomatic treatment

Introduction

Restless legs syndrome (RLS) is a common neurological disorder characterized by the occurrence of abnormal sensations usually affecting the lower extremities, accompanied by an uncomfortable urge to move, which produces transient relief. The symptoms worsen at rest and follow a circadian pattern, usually beginning in the evening or night.[1] The symptoms of RLS usually have a peak in the early part of the sleeping period (between 11 p.m. and 4 a.m. and a nadir during the early part of the waking period (between 9 a.m. and 2 p.m.).[2] The circadian pattern of RLS is now included among the diagnostic criteria.[1] Although these periodic variations in the intensity of RLS symptoms are observed in almost all subjects with mild-to-moderate RLS, there are important individual differences in the timing of symptom onset.

The onset or worsening of RLS symptoms in the evening or night, as compared to daytime, leads to insomnia, impaired sleep quality and, consequently, impaired daytime functioning, as well as mood disturbances.[1,2]

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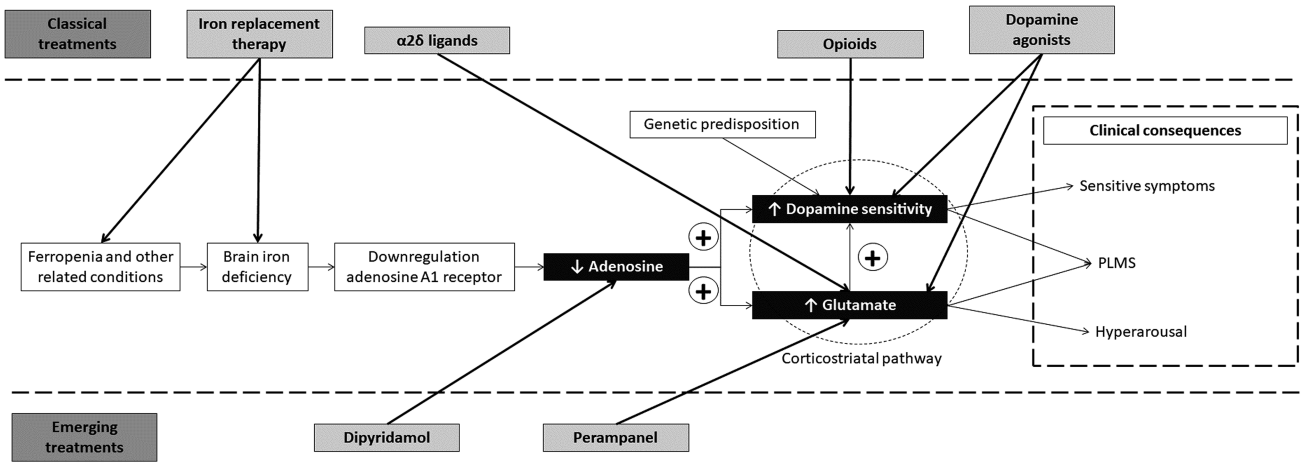

Fig. 1 Schematic presentation of the main mechanism of action for each pharmacologic treatment for restless legs syndrome (RLS), according to the pathophysiological features.

The pathophysiology of RLS has been the subject of multiple investigations in the last decades. The most recent evidence points to brain iron deficiency as a central biological abnormality in RLS, which secondarily leads to various neurotransmitter dysfunctions. Brain iron deficiency-mediated inhibition of adenosine A1 receptor (A1-R) at glutamatergic terminals induces hyperdopaminergic and hyperglutamatergic states in corticostriatal pathways.[3–5]

The treatment options for RLS are based on the aforementioned targets, according to the pathophysiology of the condition (►**Fig. 1**).[2,6]

In the present manuscript, we aim to present the current evidence regarding the physiological factors underlying the circadian pattern of RLS, briefly describe the pharmacological characteristics of RLS treatment options, and discuss how both issues should be considered in deciding the timing of administration of each drug.

Circadian Pattern in RLS Pathophysiology

Systemic Iron Metabolism

As aforementioned, cerebral iron deficiency plays a central role in the pathophysiology of RLS. It is remarkable that cerebral iron deficiency can occur despite the normal levels of systemic iron in subjects with RLS and despite the fact that no correlation between systemic iron and cerebral iron levels has been observed.[7,8]

Regarding circadian oscillations in systemic iron parameters, it has been shown that serum iron and transferrin saturation follow a circadian rhythm, with peak levels in mid-morning and a nadir at dusk and early evening, increasing during sleep. On the other hand, serum ferritin and transferrin showed no circadian pattern.[9]

Brain Iron Homeostasis

More important than peripheral iron is to elucidate what occurs in central brain iron deposits in subjects with RLS. In iron-deficient murine models, a marked circadian variation for extracellular striatal iron has been observed.[10] In 2005, Earley et al.[11] compared cerebrospinal fluid (CSF) samples obtained at 10 a.m. with those obtained at 10 p.m., and found that CSF ferritin levels were significantly lower in RLS patients, suggesting the presence of a circadian rhythm. The lack of further research on this subject is striking, although several authors have pointed out its relevance.[12]

Adenosine

Adenosine is one of the most potent regulators of the circadian rhythm (related to the S-process). During wakefulness, adenosine levels increase, and return to baseline after sleep. Under normal brain iron conditions, extracellular adenosine concentrations maintain a presynaptic inhibitory tone on glutamate and dopamine transmission, mediated by A1R. In RLS, brain iron deficiency leads to down-regulation of A1R and up-regulation of adenosine A2A receptor (A2AR). This imbalance increases the sensitivity of glutamatergic terminals, leading to hyperglutamatergic and hyperdopaminergic states. This suggests that adenosine neurotransmission may play a key role in the pathophysiology of RLS.[13]

Interestingly, shift workers suffering from RLS have been observed to change the rhythm of their symptoms, with RLS symptoms progressively coinciding with pre-sleep timing. Furthermore, regarding jet lag, westbound flights are associated with a phase delay of RLS symptoms and eastbound flights, with the opposite.[14] A hypothetical explanation for these findings could be the circadian variations in adenosine.

Dopamine

Current evidence on the role of dopamine in RLS points to a presynaptic hyperdopaminergic state, with increased dopamine synthesis and release.[13,15] Circadian variation in dopamine release has been observed, with a pattern characterized by an increase in the morning and a nadir in the late evening/night.[16] In a 22-hour study[17] in which CSF dopamine, homovanillic acid, dihydroxyphenylacetic acid, and 5-hydroxyindolacetic acid were monitored in subjects with RLS and controls, dopamine showed a peak at 10 a.m. and homovanillic acid, at 2 p.m.

The previously described circadian pattern in RLS symptoms could be linked to dopamine fluctuations. Interestingly, dopamine nadir levels in the late evening will coincide with

the appearance of RLS symptoms. Dopamine levels falling below a critical threshold would trigger RLS symptoms.[13] This would explain the clinical response to dopamine agonists (DAs) administered in the late evening or night.[12] In fact, the clinical response to DAs is included among the supportive criteria for RLS.[18]

Despite the aforementioned information, long-term exposure to DAs has been linked to a devastating iatrogenic effect known as the augmentation phenomenon. When augmentation occurs, RLS symptoms become more intense, begin earlier in the day, have a shorter latency when at rest, with a shorter relief time, and may spread to other regions of the body that were previously unaffected.[19] Augmentation could also be defined as a paradoxical effect of DAs, in which an increase in dose leads to a worsening of the symptoms, while a reduction leads to an improvement.[12] Under dopaminergic treatment, endogenous dopamine circadian rhythms may be disrupted, pushing dopamine levels below the described critical threshold for RLS symptoms. Hypothetically, this would also explain why long-acting DAs may cause less augmentation compared to short-acting DAs, as long-acting DAs may better resemble the endogenous fluctuations in dopamine levels.[19]

Glutamate

Glutamate is the main excitatory amino acid of the central nervous system. A hyperglutaminergic state has been demonstrated in RLS and has been linked to the sensory disturbances and hyperactivation that occur in this disorder. In the brain iron deficiency rodent model of RLS, increased sensitivity of cortical pyramidal cells to release glutamate from their striatal nerve terminals has been found.[20] This is probably mediated by the imbalance in adenosine A1R and A2AR.[5,13]

In addition, there is increasing evidence that glutamate transporters are controlled by the circadian system directly and indirectly. Since the discovery of the so-called "clock genes", several of them have been found to be part of the circadian regulation of intracellular glutamate through transcription-translation feedback loops.[21]

However, to our knowledge, no specific research has been conducted in subjects with RLS.

Endogenous Opioids

Although opioids have demonstrated efficacy in the treatment of RLS, few studies have yet evaluated the role of the endogenous opioid system in the pathophysiology of RLS. It is believed that the hyperdopaminergic state of RLS may lead to a decrease in endogenous opioids, which may contribute to abnormal processing of sensory stimuli.[22] On the other hand, stimulation of opioid receptors, especially mu receptors, which are strongly associated with dopaminergic receptors, facilitates dopamine release, as observed in microdialysis studies in mice and in functional imaging of dopaminergic receptor occupancy in humans.[23,24]

In a postmortem study[24] conducted in patients with RLS compared to controls, it was observed that, in the thalamus, beta-endorphin-positive cells were reduced by 37.5%, and metencephalin cells, by 26.4%. Regarding the circadian rhythmicity of opioids, a significant rhythm with a peak at 10 p.m. in the absence of time signals has been observed in a murine model.[25] Unfortunately, more research is needed in this regard in patients with RLS.

Pharmacological Considerations of RLS Treatments

Regarding RLS treatment, several therapeutical targets have been identified, and the treatments can be classified in three categories: iron replacement therapy, classic symptomatic treatments (including alpha 2 delta [α2δ] ligands, dopamine agonists and opioids) and emerging symptomatic treatments (perampanel and dipyridamole), as summarized in ►**Figure 1**.

The most updated guidelines for the general RLS treatment are from 2016,[19] and those for iron replacement therapy in RLS are from 2018.[26] Based on these guidelines, ►**Table 1** summarizes the recommendations still in force for symptomatic treatments, including information regarding the initial dose, titration, the maximum recommended dose, the usual effective daily dose, the time to peak, half-life and the recommended time of administration of every drug.

Discussion

As described, RLS symptoms follow a circadian pattern, and this fact is currently included among the diagnostic criteria.[18] Although significant progress has been made in recent decades in understanding the pathophysiology of RLS, research evaluating the ultimate drivers of circadian rhythmicity is still very limited.

Current evidence suggests that the variation in the onset and intensity of RLS symptoms over 24 hours could probably be mediated by intrinsic circadian oscillations in neurotransmitter signaling involved in the pathophysiology of RLS (systemic iron metabolism, brain iron, adenosine, dopamine, glutamate, and endogenous opioids). Overall, these circadian oscillations show a "higher-risk zone" in the first part of the sleep period (between 11 p.m. and 4 a.m.), and a "protective zone" from 9 a.m. to 2 p.m.,[12] although particular differences may exist individually. In addition, subjects with mild-to-moderate RLS suffer or not from RLS symptoms depending on the time of day, resembling an above-threshold state periodically followed by a below-threshold state (►**Fig. 2**). According to current evidence, it is crucial to investigate how to act on circadian factors in RLS, trying to establish a protective state below the threshold on a case-by-case basis.

On the other hand, considering the circadian pattern of RLS is also essential to increase the therapeutic benefit of the drugs available. The 2016 guidelines recommend a regimen of approximately 1-3 hours before bedtime for most symptomatic RLS treatments (see ►**Table 1**). However, as is often observed in the daily clinical practice, most RLS patients present with symptoms already in the early evening, or even in the afternoon. Therefore, administering the symptomatic treatment only 1 to 3 hours before bedtime will not eliminate previous symptoms and, moreover, will not help prevent the

Table 1 Summary of dosage, administration, and pharmacokinetic details for symptomatic treatments in RLS (including alpha 2 delta [α2δ] ligands, dopamine agonists and opioids).[19,24,27]

Preparation	Initial dose (mg/day)	Titration	Maximum recommended dose (mg/day)	Usual effective daily dose (mg)	Time to peak	Half-life	Recommended time of administration	Neurotransmitter target
Gabapentin	300	Increase 300 mg/day every 2 or 3 days	2,400	900–2,400	2–4 hours	5–7 hours	2 hours before bedtime	Glutamate
Pregabalin	75	Increase 75 mg/day every 2 or 3 days	450	150–450	1.5 hours	6.3 hours	2 hours before bedtime	Glutamate
Gabapentin enacarbil	600	The dose may be doubled after 1 week	1200	600–1200	5–7.3 hours	5–6 hours	5:00–7:00 p.m.	Glutamate
Immediate-release pramipexole	0.125	The dose may be doubled every 4–7 days	0.75	0.18–0.54	~ 2 hours	~ 8.5 hours	2–3 hours before bedtime	Dopamine
Immediate-release ropinirole	0.25	The dose may be doubled after 2 days and titrated upward in increments of 0.5 mg every week	4	2	~ 1–2 hours	~ 6 hours	1–3 hours before bedtime	Dopamine
Rotigotine (transdermal patch)	1	1 mg every day; the dose may be increased by 1 mg/day every week	3	2	15–18 hours; can occur 4 to 27 hours after application	After removal of the patch: ~ 5–7 hours	Replace it every day, preferably at the same time	Dopamine
Prolonged-release oxycodone*	5–10	5 mg/week	60	10–40	~ 3 hours	~ 4.5 hours	2 hours before bedtime	Glutamate
Methadone	2.5–5	2.5 mg/week	60	5–30	~ 1–5 hours	~ 15–60 hours	Not available	Glutamate

Note: *May be combined with naltrexone.

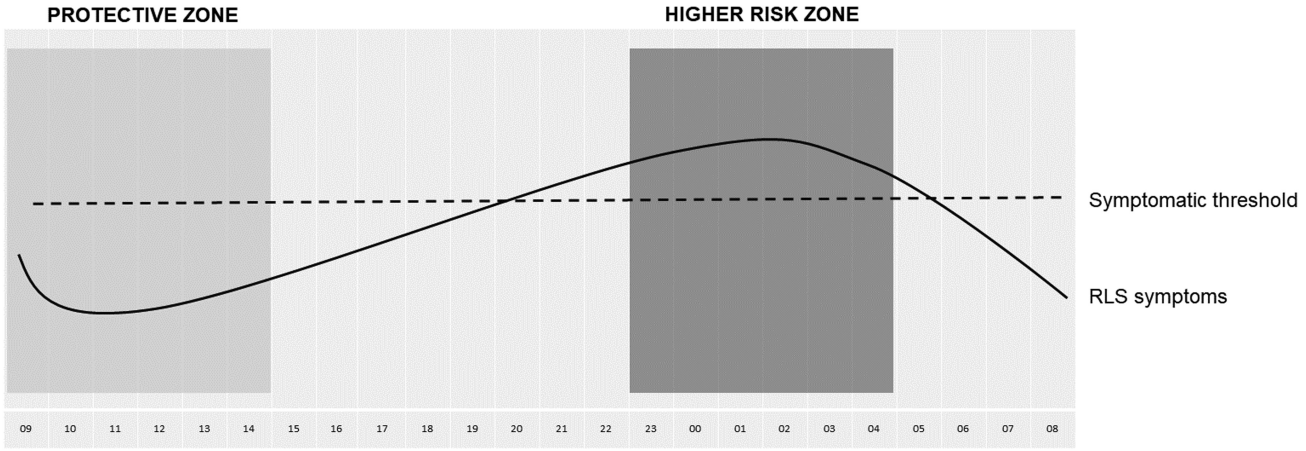

Fig. 2 Variations of restless legs syndrome (RLS) symptoms along a 24-hour model. The 24 hours are represented in the x-axis. The grey line represents the circadian fluctuations in RLS symptoms. The dotted line represents the symptomatic threshold. According to the circadian pattern of RLS, a "protective zone" and a "higher-risk zone" are represented. This figure illustrates the over-the-threshold state followed by an under-the-threshold state that periodically occurs in RLS.

circadian neurotransmitter imbalance that occurs in RLS. In conclusion, this dosage seems too late for optimal clinical benefit. Instead, we would recommend taking symptomatic drugs several hours before the onset of RLS symptoms, depending on the time to peak of the selected drug (such as 2 to 4 hours before the onset of RLS symptoms for gabapentin). It is important to note that the circadian threshold for RLS symptoms differs among individuals, and that this threshold can change over weeks, months, or years. Therefore, it is essential to ask the patient about the time of symptom onset to optimize the timing of drug administration. This should be done at each visit during clinical follow-up.

Nevertheless, while the present article aims to propose the inclusion of the circadian pattern of RLS symptoms to better adjust dosage on an individual basis, further research is needed to assess, in a controlled manner, what might be the best dosage for each symptomatic drug based on circadian variations in RLS symptoms.

Conclusions

Although the circadian pattern in RLS is well recognized as a feature of this disorder and is considered one of the diagnostic criteria, there is still a great lack of knowledge about the ultimate circadian variations of the neurotransmitters involved in the pathophysiology of RLS. The present article reviews the current evidence regarding circadian oscillations of systemic iron, brain iron, adenosine, dopamine, glutamate, and endogenous opioids; however, additional research is needed in this respect. Most RLS subjects show an above-threshold state periodically followed by a below-threshold state, determining the presence or the absence of RLS symptoms, making the circadian oscillations crucial. In this context, it is also essential to consider circadian variations in the pathophysiology of RLS to better adjust the dosage of available RLS treatments. The latest 2016 guidelines recommend a regimen of approximately 1 to 3 hours before bedtime for most symptomatic RLS treatments; however, this dosage seems too late for the optimal clinical benefit, as most subjects already eel RLS symptoms before that time. We would recommend anticipating the drug intake to the onset of RLS symptoms individually, according to the time to peak of each drug, so that drugs could help balance the neurotransmitter fluctuations, preventing symptom onset.

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Conflict of Interests
The authors have no conflict of interests to declare.

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