Dopamine Agonists in the Treatment of Restless Legs Syndrome: Too Much of a Good Thing?

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INTRODUCTION

Restless legs syndrome (RLS) is one of the most common sleep-related sensorimotor disorders, with an estimated prevalence of 8%–10% in the general adult population of Europe and North America. The syndrome is characterized by irresistible restlessness and an urge to move the legs (although the upper limbs may also be involved), particularly in the evening. This urge is often accompanied by unpleasant “prickly”, “stinging”, “creeping” or “burning” sensations. In 1995, the International Restless Legs Syndrome Study Group issued guidelines on the diagnosis of RLS. These guidelines were recently updated. The five key diagnostic criteria for RLS (all of which must be met) are 1) an irresistible urge to move the legs, usually but not always accompanied by uncomfortable and unpleasant sensations in the legs, 2) symptoms that begin or worsen during periods of rest or inactivity, such as lying down or sitting, 3) symptoms that are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, 4) symptoms that only occur in the evening or night or are worse in the evening or night than during the day, and 5) the occurrence of the above features is not solely due to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, and habitual foot tapping).

RLS can be categorized as primary (idiopathic) or secondary. Primary RLS has a strong genetic component because a first-degree family history is reported in up to 60% of the patients. Secondary RLS is known to result from comorbid conditions, such as iron deficiency, kidney failure, diabetes, or treatment with certain medications. The underlying mechanism in RLS is thought to include a dysfunction in the dopaminergic system and a brain iron deficiency in genetically predisposed individuals. Brain iron deficiency sometimes has a peripheral cause and is revealed by anemia and/or hypoferritinemia. The main consequence of brain iron deficiency is hypoxia, which leads to 1) a presynaptic hyperdopaminergic state (with an increase in the synthesis, liberation, and turnover of dopamine), and 2) myelin loss and white matter alterations. These intracerebral disorders lead to the dysfunction of the sensorimotor loop at various levels of integration. The descending dopaminergic system (which inhibits the posterior horn of the spinal cord) is particularly affected. It is thought that the inhibitory control of sensory afferents is impaired in individuals with RLS. This impairment results in various sensory disorders, which are partially corrected by movement. Predominantly, lumbosa-
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cranial spinal hyperexcitability causes periodic movement during wakefulness.\(^\text{10}\)

**DOPAMINERGIC THERAPY IN RLS**

In the early 1980s, it was found that patients with RLS had a marked response to dopaminergic agents (first levodopa and dopamine agonists [DAs]). DAs such as pramipexole, ropinirole, and rotigotine have been the mainstays of RLS treatment.\(^\text{11}\) These findings initially suggested the presence of an intracerebral hypodopaminergic state. A series of randomized, controlled trials led to the approval of DAs by the US Food and Drug Administration for the indication of RLS.\(^\text{12}\) However, the vast majority of clinical and brain imaging studies carried out over the last decade have revealed a paradoxical, presynaptic, and hyperdopaminergic state.\(^\text{9}\) This realization explains why DAs are highly effective for short-term pain relief in patients with RLS but have mid-term and long-term side effects\(^\text{13}\): the most significant of which are augmentation syndrome (AS), characterized by an increase in both symptom severity and intensity, and a temporal and spatial progression of RLS symptoms; the latter starts earlier in the afternoon and spreads to previously unaffected parts of the body, especially the arms. AS is common during treatment with DAs: the annual incidence rate is around 8% for pramipexole and ropinirole, and the 10-year cumulative prevalence is around 50%.\(^\text{14}\) Furthermore, the results of several studies have suggested that this prevalence is continuing to rise.\(^\text{15}\) Treatment with DAs has sometimes other serious side effects (regardless of the treatment duration): 1) excessive daytime sleepiness with sleep attacks, with harmful consequences like drowsiness when driving and motor vehicle collisions, and 2) impulse-control disorder symptoms, including a spectrum of undesirable behaviors such as compulsive and financially destructive shopping, gambling, punding (repetitive, aimless hand movements, such as the disassembly and reassembly of watches or other gadgets), and other quasi-addictive behaviors,\(^\text{13}\) with sometimes disastrous medical and legal consequences.\(^\text{16}\) The occurrence of the painful symptoms of RLS is related to nocturnal dopamine production (Fig. 1). Dopamine secretion has a circadian rhythm\(^\text{17}\); it decreases during the evening and night and increases in the morning. Hence, dopamine levels are often sufficient during the day but not at night. When a DA is prescribed, a small dose taken in the evening or at night can initially correct the evening fall in dopamine levels. However, in the mid- to long-term period, this leads to greater downregulation, worse RLS symptoms, and the requirement for higher doses of DA for effectiveness. Ultimately, this treatment worsens the underlying disease, leading to AS.

**WHY IS TAKING A DA NOT LOGICAL FROM A PATHOPHYSIOLOGICAL POINT OF VIEW?**

To better understand why taking DA in RLS can cause the side effects as described above, we need to look at the basic physiology of RLS, even though our knowledge is only partial.\(^\text{18}\) There are two main families of dopamine receptors: D1 and D2. Both families are abundant in the dorsal striatum and are affected by RLS. Neurons expressing D1 receptors are the
main components of the direct striatopallidal pathway and have an excitatory action. Conversely, striatal neurons expressing D2 receptors are involved in the indirect striatopallidal pathway and have an inhibitory action. Furthermore, some D2 receptors are presynaptic; therefore, have negative feedback control over dopamine release. Under normal physiological conditions, concomitant stimulation of the D1 and D2 receptors is required for normal functioning of the descending hypothalamic pathway, sensorimotor cortex excitability, and somatosensory integration (Fig. 2). In RLS, a presynaptic hyperdopaminergic state might lead to the internalization of postsynaptic D2 receptors; the more the dopaminergic system is stimulated (for example, by high doses of DAs), the more postsynaptic D2 receptors are internalized. A preferential decrease in the number of D2 receptors on the postsynaptic cell membrane induces an increase in the number of D1 receptors. This imbalance in the D1/D2 synergism leads to the proliferation of D1 receptors. Chronic hyperstimulation of D1 receptors and unstable dopamine metabolism might lead to an impairment in the descending dopaminergic pathway (involving the dorsoposterior hypothalamus and the spinal cord) or greater sensorymotor cortex excitability and thus the appearance of AS.9

However, dopamine receptor function is very complex, and other factors may affect susceptibility to disease or an individual patient’s response to medications. These factors include polymorphisms in genes encoding dopamine receptors and other proteins involved in dopamine transmission (such as G proteins, dopamine receptor-interacting proteins, G protein-coupled receptor kinases, and arrestins).19

Finally, other neurotransmitters (such as adenosine and glutamate) appear to be involved in the pathophysiology of RLS.20

**ALTERNATIVE TREATMENT OPTIONS FOR RLS**

At present, both DAs and some anti-epileptics (such as alpha2delta ligands) are being utilized as first-line treatments for RLS.21 Considering the potential side effects of DA, first-line treatment of RLS with this drug class—the only currently authorized treatment for this indication in France—should no longer be the rule.22 Among the alpha2delta ligands, gabapentin demonstrates improvement in RLS symptoms with level A evidence and presents advantages in terms of sleep quality.22 It is challenging to assert the effectiveness of alpha2delta ligands compared to that of DAs, as stating their superiority in terms of efficacy is difficult. There is evidence suggesting that alpha2delta ligands may be less effective in patients with non-augmented RLS who were previously treated with DAs, possibly due to a hyper-glutaminergic state.23 World Health Organization step 2 opioids (essentially tramadol) can also be used (particularly in mild forms of the disease) on an on-demand basis, in order to avoid their frequent side effects (e.g., constipation, sedation, and the onset or aggravation of respiratory problems) and a risk of addiction in predisposed patients.24

In the coming years, other drugs acting on non-dopaminergic pathways may reinforce this weak therapeutic arsenal. In a clinical study published in 2017, perampanel (α-mino-3-hydroxy-5-methyl-4-isoxazolopropanoic acid, a selective glutamate receptor antagonist) showed efficacy in a small series (n=20) of...
patients with RLS: after an 8-week course of treatment at a mean dose of 3.8 mg/day, the International Restless Legs Syndrome Study Group rating scale (IRLS) score had fallen from 23.7 (out of 40) to 11.5.23,25 Twelve of the 20 patients were classified as “full responders” (i.e. with an improvement of 50% in the overall IRLS score), and four were classified as partial responders. In 2018, the same researchers reported a study of dipyridamole (a non-selective antagonist of equilibrative nucleoside transporters 1 and 2) in 13 patients.27 The mean IRLS score fell from 23.4 at baseline to 10.7 after an 8-week treatment period. Six of the 13 patients were classified as full responders and four were classified as partial responders. The efficacy, safety, and tolerability of these new symptomatic treatment approaches for RLS require further investigations in larger populations.

Lastly, medicinal mushrooms such as *Ganoderma lucidum* (GL) might also have therapeutic value.28-30 Recently, a preliminary study of 18 consecutive patients with primary RLS in a private neurology practice, assessed the effects of treatment with GL extract (920 mg) daily for 2 months.31 The IRLS scores after 1 and 2 months of treatment were significantly lower than the baseline values. Thirteen patients (72%) reported relief after 2 months of GL treatment, and relief was maintained in 11 patients (61%) 2 weeks after GL discontinuation.

CONCLUSION

RLS is a common pathology that lacks satisfactory treatment options. There is a need to rethink the treatment strategies for RLS and limit the prescription of DAs; the latter aggravates the underlying disease mechanisms in RLS and has side effects (such as AS) that are difficult to manage. Medications acting on dopamine neuro modulation and systems other than the dopaminergic pathway may also be effective.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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Funding Statement

None

Acknowledgments

I thank Virginie Denis for her illustration assistance.

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