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Sleep Disorders (A Iranzo, Section Editor)

Therapies for Restless Legs in Parkinson's Disease

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Abstract

Purpose of review The aim of this article was to review the options and particularities of the treatment of restless legs syndrome (RLS) in Parkinson's disease (PD).
Recent findings RLS is more frequent in PD than in the general population. Even if these two disorders share some specificity (dopa-sensitivity), they also differ in many features (iron load, genetic profile, dopaminergic cell count), resulting in different adaptations of the treatment. Only one study has specifically explored and demonstrated the efficacy of a treatment (rotigotine) in RLS with PD, constraining us to treat RLS with PD by analogy as idiopathic RLS in the other cases. However, arrangements linked to the peculiar population and pathology of PD are required.
Summary The treatment of RLS in PD consists in adaptation of dopaminergic treatment and introduction of alpha-2-delta ligands and, in refractory cases, of opioids or deep brain stimulation. Iron deficiency should probably not be compensated.

Introduction

Sleep disorders are one of the most disabling non-motor symptoms of Parkinson's disease (PD). Among them, restless legs syndrome (RLS) is frequent and sometimes very challenging for its diagnosis and treatment (Fig. 1).

RLS is defined by an urge to move principally the legs, sometimes associated with paresthesia, occurring or worsening at rest, in the evening, or at night. It is relieved by activity [1]. PD is a complex neurodegenerative movement disorder defined clinically by rigidity, bradykinesia, and tremor, but also associated with multiple non-motor sensory, autonomic, and sleep symptoms [2].

Different studies have demonstrated that RLS is more common in PD (10–50%) [3–6] than in the general population (2.5–10%) [7, 8]. Idiopathic RLS does not seem to precede the development of PD. Usually, PD presents itself first, and RLS is one of the non-motor features associated with it. In the de novo untreated

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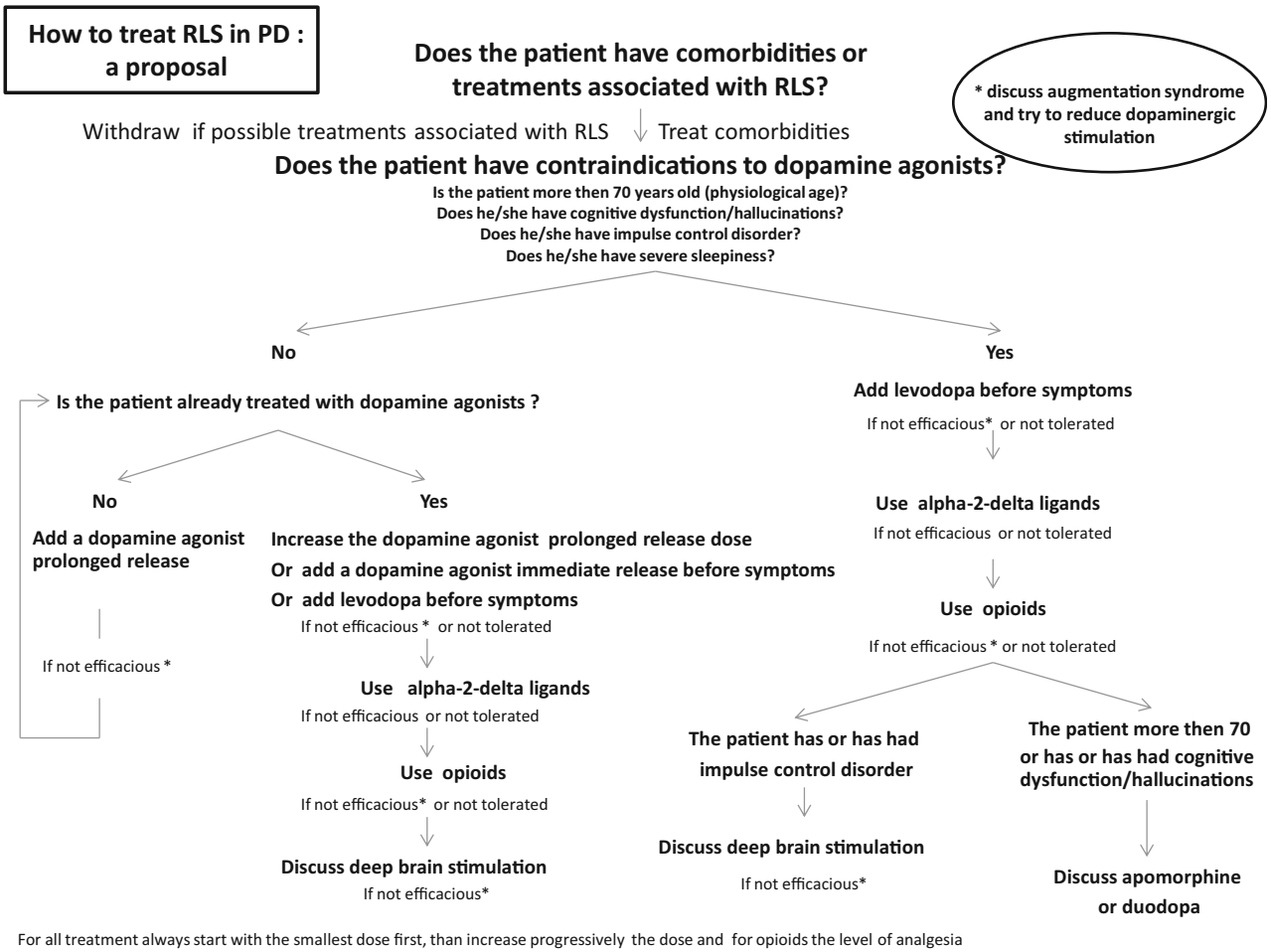

Fig. 1. Different treatment options for RLS in PD.

populations, the prevalence of RLS seems to be similar to that of controls across populations. Then, RLS prevalence increases during the course of PD and treatment duration, independent of the drug dosages [9]. The dopaminergic therapy may though have a crucial role in the development of RLS in PD patients.

RLS and PD share several features that impact on their treatment. They are responsive to dopaminergic pharmacotherapy to the extent that it represents a diagnostic criterion for both diseases. On the other hand, both may have complications to this dopaminergic stimulation such as dyskinesia for PD and augmentation syndrome for RLS. Augmentation syndrome refers to a paradoxical treatment-related increase in RLS symptoms. It has been described with all dopaminergic treatments. Finally, both are associated with periodic limb movements of sleep (PLMS) [10]. PLMS are stereotypic, repetitive, non-epileptiform movements of the legs, usually consisting of dorsiflexion of the ankle. They are usually reported by the co-sleeper and confirmed by sleep recordings. They often increase sleep fragmentation. PLMS are associated with RLS in 80% of the patients [11]. Most studies report also higher rates of PLMS in PD [10]. Many studies on the efficacy of the treatment of RLS use the reduction of PLMS index during the night as a criterion of efficacy.

On the other hand, numerous features differentiate idiopathic RLS and PD that may also influence RLS treatment in PD. When PD results mainly from the dopaminergic neuronal loss in the substantia nigra and subsequent abnormal function in the nigrostriatal pathway, in idiopathic RLS, postmortem studies have demonstrated no dopaminergic cell loss nor reduction in dopamine content [12] and brain imaging studies have

revealed an increase in presynaptic dopaminergic activity [13, 14]. PD is associated with increased iron in dopaminergic areas when primary RLS is associated with reduced intracellular iron measured post mortem [15, 16]. Finally, different studies have demonstrated that RLS genetic risk markers are not associated with increased PD risk or subtype [17, 18].

All these elements suggest that idiopathic RLS and RLS occurring in patients with PD could possibly have different pathogenesis; therefore, treatment success in idiopathic RLS might not be directly applicable to treatment of RLS associated with PD. However, most of the studies on the treatment of RLS focus on idiopathic RLS. Studies on the treatment of RLS associated with PD are so scarce that we, in clinical practice, use the same strategy as for idiopathic RLS, using however some precautions that we will develop.

The efficacy of the treatments in idiopathic RLS is usually measured by an improvement in the severity of the symptoms evaluated by the International RLS (IRLS) Study Group Rating Scale [19] (on which the score ranges from 0 to 40, with a higher score indicating more severe symptoms) or the Clinical Global Impression of Improvement scale (which is used to assess the proportion of patients with symptoms that were "very much improved" or "much improved"). Many studies on the efficacy of the treatment of RLS have also used the reduction of PLMS index during the night and the improvement in sleep quality (reduced sleep fragmentation, improved sleep efficacy…) as a criterion of efficacy. However, these measures have not been validated in PD except for the modified PD Sleep Scale (PDSS-2) that explores sleep disorders in PD, with specific items oriented on RLS symptoms [20]. Finally, suggested immobilization test, a more objective measure of RLS that assesses both subjective leg discomfort and objective leg movements during a 1-h period of immobility prior to bedtime, has been validated in RLS with PD [21], but has regrettably never been used to our knowledge to evaluate the efficacy of a treatment in this peculiar condition.

Comorbidities and treatments associated with RLS

As in idiopathic RLS, in RLS with PD, other secondary factors and contributing comorbidities of RLS should be excluded. Metabolic disorders, end-stage renal disease, diabetes, pregnancy, and other sleep disorders should be explored and treated if needed. RLS symptoms can be side effects of medications including some antidepressants, neuroleptics, and tramadol hydrochloride [22] that should be withdrawn if possible.

Iron

Different authors have suggested to check for serum ferritin and if serum level is lower than 50–75 ng/ml to prescribe oral iron supplementation [23]. If oral iron is poorly tolerated or contraindicated, the intravenous administration can also be considered [24]. However, no study has ever tested this supplementation, and it is not known whether this could affect the course PD. This supplementation is questionable since there is growing evidence that PD is associated with oxidative damage via iron accumulation in the substantia nigra and recent studies have suggested an improvement of PD with iron chelators [25]. It is actually very arguable to prescribe iron supplementation in this population.

Dopaminergic agents

Dopamine agonists and levodopa improve RLS as well as PD, so adjustment of these medications in PD may improve RLS. Levodopa and other short-acting dopaminergic agents may increase the risk to develop augmentation syndrome. To prevent this phenomenon, the lowest possible effective dose of dopaminergic agents and the most continuous delivery are recommended in RLS [26••]. In the same way, to prevent dyskinesia and motor fluctuations, the same recommendations are given in PD. Dopamine agonists allow the most continuous dopaminergic stimulation, so that they should be preferred. However, they are not always well tolerated.

Levodopa

In patients with PD and older age, cognitive dysfunction, or impulse control disorder, dopamine agonists should be avoided and only levodopa can be used. In this condition, the treatment of RLS consists in an optimization of the levodopa intakes schedule, especially adding intakes in the evening and during the night. Most patients with PD have multiple, sometimes prolonged arousals during the night. Adding a supplementary levodopa intake during these episodes represents little constraint for them and in our experience is efficacious to reduce RLS rebounds in the early morning.

Levodopa-carbidopa intestinal gel, treatment indicated in advanced PD, allows continuous dopaminergic stimulation and is efficacious in the treatment of PD symptoms. This treatment is usually only prescribed during the day. A recent case report has shown its

usefulness in a case of refractory idiopathic RLS with a 24 h/day infusion [27]. This continuous infusion should be proposed in patients with PD and treated with this treatment the whole day only and could be proposed in patients with PD and refractory RLS.

Dopamine agonists

Rotigotine (2–3 mg), ropinirole (0.78–4.6 mg), pramipexole (0.25–0.75 mg), cabergoline (2–3 mg), and pergolide have demonstrated their efficacy in the treatment of idiopathic RLS [26••]. Monitoring of augmentation is recommended for all these treatments [26••]. Side effects, especially sleepiness, confusion, hallucinations, and impulse control disorders, must be under close supervision in this population of mostly older adults but also already largely stimulated on their dopaminergic pathways.

Ergot-derived dopamine agonists (cabergoline and pergolide) are not first-choice therapies because they have induced cardiopulmonary fibrosis and though justify special monitoring.

Ropinirole and pramipexole

We have been using these treatments, in their immediate release form, in PD, for a long time. Their short-acting efficacy (a few hours) may be interesting in RLS with PD: they can be efficacious when needed (during the evening or at night) but not during the day, reducing some side effects (sleepiness, hallucinations, and sometimes impulse control disorders). The smallest dose of ropinirole or pramipexole, 2 h before the RLS symptoms, may be very efficacious and well tolerated in our experience, even in patients with PD in which dopamine agonists were not our first choice.

When patients with PD can be treated with dopamine agonists without obvious contra-indication, then, prolonged release is preferred in order to reduce the augmentation syndrome risk.

Rotigotine

The efficacy of rotigotine on RLS symptoms in PD has been demonstrated in four open studies [28–31] and one randomized control trial [32••]. In this double-bind, placebo-controlled trial, RECOVER, a large number of patients with PD and early-morning motor symptom complaints received rotigotine (2–16 mg/24 h, $n = 190$) or placebo ($n = 97$). Rotigotine was associated with a significantly greater improvement on both the motor symptoms of PD (reduction in UPDRS part III score −3.55, $P = 0.0002$) and the evaluation of sleep complaints (reduction in PDSS-2 −4.26, $P < 0.0001$) than placebo. The "restlessness of arms and legs", "urge to move arms or legs", and "uncomfortable and immobile" were among the most improved individual PDSS-2 items, demonstrating a strong effect on RLS symptoms.

Twenty-four-hour transdermal delivery of rotigotine was associated with adverse events (nausea, application site reactions, and dizziness). Some authors have suggested, in order to reduce these events, to use the treatment only at night [30].

Continuous apomorphine infusion

The efficacy of continuous apomorphine infusion on sleep disorders in PD has been reported in a few studies. One placebo-controlled study has demonstrated an improvement of pain scores and the number of spasms and of awakenings in patients with PD ($n = 6$) and RLS ($n = 2$) and one patient with both [33]. Another one without control group but with sleep measures has demonstrated reduction of periodic limb movement and an improvement in sleep microstructure with transdermal apomorphine treatment [34]. More recently, the study ApoNight demonstrated an improvement in sleep complaints in patients receiving apomorphine during the night. However, no details were given on subscores dedicated to RLS. Further studies are needed to confirm this efficacy.

Alpha-2-delta ligands

Gabapentin, gabapentin enacarbil, and pregabalin have demonstrated more or equivalent efficacy than dopamine agonists in idiopathic RLS without the dopaminergic problems of augmentation, impulse control disorder, severe sleepiness, and hallucinations [26••, 35]. Even if they have largely been studied and used in idiopathic RLS, studies on their efficacy in RLS associated with PD are lacking. They may be preferentially effective in patients whose RLS symptomatology is focused on sensory discomforts. This particularity could be very helpful in PD where neuropathic pain is frequently reported [36, 37]. Their sedative aspect might especially be helpful in patients with RLS emergent primarily at sleep onset or with an additional insomnia. On the other end, it might increase the sleepiness associated with PD during the day [38].

Gabapentin

Gabapentin is the first alpha-2-delta ligand to have demonstrated its efficacy in idiopathic RLS [39]. Efficacious at a dose of 800 mg in divided doses, its side effects are fairly common. Especially frequent in older patients, they associate dizziness, sleepiness, and peripheral edema in a dose-dependent way [26••]. Introduced at slowly increasing doses until efficacy with a careful supervision of side effects, gabapentin is a useful treatment of RLS associated with PD in our clinical practice.

Pregabalin

Pregabalin is also efficacious for the treatment of moderate to severe idiopathic RLS when given at doses between 150 and 450 mg/day, 1 to 3 h before bedtime [26••, 40–42]. Side effects of pregabalin associate dizziness, somnolence, fatigue, and headache and appear to be dose-related [41]. Even if it has not proven efficacy in RLS with PD yet, in our experience, it is useful and usually well tolerated if introduced at progressive doses. Notice however that a case was reported of full-blown parkinsonism induced by pregabalin. The syndrome completely resolved 3 months after withdrawal [43]. Two other case reports described dyskinesia (one with bilateral ballism) induced by pregabalin in patients with PD [44, 45]. These two cases suggest the surveillance of the movement disorders after introduction of pregabalin in patients with PD. The increase in the motor symptoms or the appearance of dyskinesia should induce a therapeutic window of pregabalin to challenge the imputability of the treatment in these clinical modifications.

Gabapentin enacarbil

Gabapentin enacarbil, a prodrug of gabapentin, is the last alpha-2-delta ligand having demonstrated its efficacy for the treatment of moderate to severe idiopathic RLS [26••, 46–52]. The optimal dose is actually validated at 1200 mg once a day. Side effects are dizziness and somnolence which should be especially monitored in older adults. One case report described its efficacy in RLS with dementia with Lewy Body [53]. Because a dopamine agonist had caused the occurrence of metamorphopsia, an alternative treatment of gabapentin enacarbil was used; this treatment improved the patient's RLS without worsening her psychiatric symptoms. Not available in France, we have no experience on this treatment.

Opioids

Two randomized trials have demonstrated the efficacy of opioids in the treatment of refractory idiopathic RLS [54, 55]. Refractory RLS is characterized by unresponsiveness to dopamine agonists or alpha-2-delta ligands due to inadequate efficacy, augmentation, or adverse effects. The first study explored the efficacy of oxycodone versus placebo in 11 patients in a double-blind cross over trial. Efficacy on leg discomfort, urge to move, PLMs index, number of awakenings, and sleep efficiency was obtained with divided night-time doses (2 h prior to bedtime, at bedtime, and in the middle of the night) at an average dose of 15.9 mg of oxycodone [54]. One patient complained about a lethargy that improved with a dose reduction. Two patients deplored constipation. No increase in the sleep apnea/hypopnea index or in oxygen saturation measures were observed on sleep recordings. The second study explored the efficacy of oxycodone/naloxone versus placebo in a large randomized study in 306 patients with severe idiopathic RLS and previous unsuccessful treatment [55]. The fixed-dose combination of prolonged-release oxycodone/naloxone was chosen in order to reduce the well-known bowel dysfunction associated with oxycodone alone. Drug titration started with oxycodone 5 mg, naloxone 2.5 mg, twice per day, which was up-titrated according to investigator's opinion to a maximum of oxycodone 40 mg and naloxone 20 mg, twice per day. After 12 weeks, oxycodone/naloxone resulted in a greater symptom reduction on IRLS (-16.5 ± 11.3) than placebo (-9.4 ± 10.9) with mean difference between groups of 8.15 (95% CI 5.46–10.85; $p < 0{\cdot}0001$). The mean dose of oxycodone was 21.9 ± 15.0 mg and that of naloxone of 11.0 ± 7.5 mg. Treatment-related gastrointestinal disorders, nervous system disorders, fatigue, and pruritus were more common in the prolonged-release oxycodone–naloxone group than in the placebo group. Clinically relevant constipation was reported in 12 (8%) of 150 patients as an adverse event during the double-blind phase.

No study has explored to date the efficacy of opioids for RLS in PD. However, prolonged-release oxycodone–naloxone has also been used to reduce different types of chronic pain in patients with PD in a large randomized study [56]. Responders for average 24-h pain at 16 weeks (≥ 30% reduction from baseline) were more common in the oxycodone/naloxone group (42/88 patients; 48%)

than in the placebo group (36/106 patients; 34%; $p = 0 \cdot 021$), and responders for CGI-I were more common with oxycodone/naloxone (32/88 patients; 36%) than with placebo (28/105; 27%; $p = 0 \cdot 019$). Nausea and constipation were seen more frequently under treatment. No opiate-induced deterioration in motor function has been observed. Even if RLS is a distinct disorder, differing from chronic pain in many ways, the use and the tolerance of these drugs in this population is very informative.

All in all, as in idiopathic RLS [57], in refractory RLS associated with PD, opioids should be used. Treatment should be started with the least-potent opioid at the lower dose and be gradually increased in both dose and power. Controlled-release medication should be used for evening dosage and short-acting drugs, if needed, during the day. Effective doses for RLS treatment are considerably lower than the one used for chronic pain. Side effects such as constipation should be carefully looked after, because of their frequent presence and severity in PD. Oxycodone/naloxone should probably be preferred in order to reduce this disabling and sometimes severe side effect. A close supervision of neuropsychiatric side effects and hallucinations is also especially required in this peculiar population. Augmentation syndrome should be looked after since it has been reported with opioids [58–60].

Benzodiazepines and clonazepam

Benzodiazepines and particularly clonazepam reduce sleep latency and improve sleep continuity and, hence, intuitively are thought to be beneficial to people with RLS and frequently used. However, a Cochrane Database systematic review recently found that the effectiveness of benzodiazepines in idiopathic RLS remains unknown [61]. On the other hand, a PSG study found that patients with PD already treated with clonazepam had fewer PLMS and less daytime sleepiness than those without clonazepam [62]. In our experience, when RLS in PD is associated with insomnia and anxiety, benzodiazepines can be very useful. Further studies are needed to explore the mechanism of this improvement in patients with PD and the specific effect of benzodiazepines.

Deep brain stimulation

Sub-thalamic nucleus deep brain stimulation (STN DBS) is a well-established treatment of dopamine-responsive motor symptoms of patients with advanced PD [63]. Because RLS is improved by dopaminergic therapies, different authors have explored the efficacy of STN DBS for PD on RLS with conflicting results.

Three studies reported improvement in RLS symptoms after STN DBS in patients with PD [64–66]. One demonstrated in 6 patients a significant improvement of the IRLS scores (23.0 ± 5.8 preoperative versus 14.8 ± 5.0 at 4 weeks postoperative, $p = 0.027$, and 13.8 ± 8.6 at 6 months, $p = 0.037$) [64]; another reported an even more important improvement also in 6 patients with a reduction of the IRLS from 24.8 ± 8.3 preoperative to 4.0 ± 5.8 postoperative ($p < 0.05$) with complete resolution of symptoms in three of them. Eventually, a more recent, more prolonged, and larger study in 22 patients with PD and moderate to severe RLS also demonstrated a significant improvement of the IRLS (19.6 ± 7.0 preoperative versus 14.5 ± 12.3 at 6 months postoperative, $p = 0.03$, and 11.7 ± 8.1 at 1 year, $p = 0.005$, and 12.8 ± 11.3 at 2 years, $p = 0.003$) that lasted for up to 2 years after surgery [66]. Almost one third of the patients had complete resolution of symptoms. STN DBS was followed by a significant reduction in dopaminergic therapy (34.5–69.2%); however, there were no statistically significant correlations between improvement in the IRLS and changes in levodopa equivalent dose. The significant reduction of motor symptoms after surgery was not either correlated with the improvement of IRLS.

On the contrary, two studies have reported emergence of RLS after STN DBS one in 11 out of 195 [67] and 1 in 6 out of 31 patients [68•]. Dopaminergic therapy modifications after surgery may explain these discrepancies. Abrupt decrease of dopaminergic treatment may reveal underlying hidden RLS [67], but maintenance of high doses postoperatively could lead to dopaminergic overstimulation as in augmentation syndrome [68•].

Interestingly, lesioning of globus pallidus has also been reported to be effective in RLS in one patient with PD [69].

The mechanism involved in the improvement of RLS by DBS remains unclear. As in PD, STN stimulation could modulate the basal ganglia outflow reducing the downstream disinhibition at the spinal level, thus alleviating abnormal sensations and motor restlessness [70, 71]. Further studies are needed to explore these mechanisms (precise localization of contacts, circadian variations of the nuclei activities and neurotransmitters…) are needed to clarify the role of STN DBS on RLS in PD.

All these interesting results on the improvement of RLS in PD after STN DBS should however be interpreted

with caution. In fact, none of the studies on the subject had a placebo control, and both diseases, PD and RLS, are known to have an important placebo response [72, 73]. Moreover, the magnitude of the placebo effect is directly related to the cost and the nature of the procedure and though is especially high in brain surgeries [74].

Pneumatic compression devices

One prospective, randomized, double-blinded, sham-controlled study of pneumatic compression devices in individuals with idiopathic RLS demonstrated an improvement in IRLS (from 14.1 ± 3.9 to 8.4 ± 3.4 ($p = 0.006$)). Quality of life, sleepiness, and fatigue also improved [75•]. Subjects wore a therapeutic or sham device prior to the usual onset of symptoms for a minimum of 1 h daily. This kind of device has never been tested to our knowledge in PD but could be an alternative option to drugs in this population already receiving multiple pharmacotherapies.

Conclusion

There is no guideline today to treat RLS in PD. Most of the studies do not explore specifically the efficiency of the treatments of RLS in this peculiar population so that in clinical practice, we use the guidelines made for the treatment of idiopathic RLS and adapt them to the guidelines and our knowledge on PD treatment. This vacuity might even be deleterious since, for example, most of us did or continue to do a systematic iron supplementation in patients with iron deficiency, when this supplementation possibly contributes to neuronal death in PD. Moreover, the side effects of the treatments might be different and more severe in this frail population and need to be explored. A step by step validation of the efficacy and side effects in RLS with PD of the treatments used in idiopathic RLS are needed to finally be able to elaborate validated guidelines on the topic.

Compliance with Ethical Standards

Conflict of Interest

The author declares that she has no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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