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Editorial

Withdrawal symptoms following dopaminergic treatment of RLS

The use of dopaminergic treatments in restless legs syndrome/Willis-Ekbom disease (RLS/WED) has been generally well known over the last several decades, with three dopamine (DA) receptor agonists having been approved for the first-line treatment of RLS in most developed countries. The approval of these three drugs by the regulatory agencies was based on placebo-controlled studies, which showed therapeutic efficacy over the short-term with relatively minor toxicity [1].

However, clinical experience has shown that the practical use of dopaminergics can prove difficult due to three different complications: early-morning rebound, dopaminergic augmentation and withdrawal. The first of these, early-morning rebound, is a transitory occurrence of symptoms that typically lasts a few hours and occurs in the early to mid-morning hours [2]. It is preceded by a symptom-free period (usually during sleep) but also followed by another asymptomatic period, normally when awake, that should occur always before the usual onset of RLS later in the day. End-of-dose rebound usually coincides with the declining phase of therapeutic levels from the treating drug. Hence, it follows time to maximum plasma concentration (TMax). End-of-dose rebound is common with drugs that have a shorter half-life, such as levodopa [3]. Although rare, this becomes a problem when the approved oral dopamine agonists wiht relatively longer half-life are used [4,5].

In contrast, dopaminergic augmentation of RLS symptoms is, by far, the main complication of dopaminergic treatment [6]. This consists of an increase in symptom severity and intensity, with symptoms starting earlier in the afternoon, occupying more time over 24 h and spreading to previously unaffected areas of the body. One of the features of augmentation is the so-called paradoxical response, by which increasing doses of the medication results, over time, in a worsening in the severity of symptoms, while decreasing doses lead after some time (usually days or weeks) to an improvement in symptom severity [7]. While augmentation was initially thought to be mostly restricted to levodopa, it is also common during treatment with dopamine agonists, with an approximate yearly incidence rate of 7–8% [8]. Since augmentation is frequently a fluctuating process that tends to worsen over time, this incidence rate increases or accumulates with time. Thus, following a treatment period of approximately 10 years, the prevalence of augmentation nears 50% [9–11]. Furthermore, given that the existing data do not indicate any decrease in the incidence of augmentation with longer duration of use, it seems likely that with longer follow-up periods, prevalence might be even higher than what is known.

Unlike the two previous complications, withdrawal symptoms following treatment discontinuation, have not been well investigated. Withdrawal symptoms are well known for drugs such as benzodiazepines or opioids; and are defined as a temporary increase in the severity of the symptoms that are being treated and can last from days to weeks both during and after the drug discontinuation period. Typical symptoms occurring during rebound are vegetative symptoms such as insomnia, increased heart rate, hyperhidrosis, muscle stiffness, and constipation, etc; however, tremor or hyperalgesia can also be seen, particularly during opioid withdrawal. In the most severe cases, epileptic seizures, confusion, and even psychotic symptoms have been described [12]. If the temporary increase in symptom severity ever surpasses the severity levels reached before treatment initiation, then the correct term to be used is “overshoot”. One would anticipate in RLS that besides an increase in neurovegetative symptoms, patients would also experience an overshoot in RLS symptoms (dysesthesias and periodic limb movements in sleep [PLMS]).

In this issue of *Sleep Medicine*, Wang et al. [13], report the time course of post-withdrawal symptoms in a group of 24 patients who had tapered down dopaminergic treatment (DA group), and in an additional five patients who had gradually discontinued non-dopaminergic medication (non-DA group). In the DA group, they observed a gradual improvement of sleep-related symptoms, but also in RLS severity and duration of symptoms, during the one – eight days that followed the post-withdrawal period. In contrast, in the non-DA group symptoms were less severe at all time points and did not change over the course of time. Notably, the time of onset of RLS symptoms was not significantly different between the DA and the non-DA group. Furthermore, DA-treated patients had higher rates of PLMS than non-DA at all times, and in both groups, the frequency of PLMS remained barely constant over the entire period.

While dopamine agonist withdrawal syndrome is a well-recognized entity in Parkinson's disease (PD) where it can affect up to 19% of patients [14], the issue has not been sufficiently investigated in RLS.

The study by Wang et al., presents intriguing data but, as acknowledged by the authors, contains a number of methodological shortcomings that need to be taken into consideration: thus, according to the definition of withdrawal, a baseline evaluation during treatment is required, and none was obtained here. In addition, no data are presented on the discontinuation period, only in the post-withdrawal phase. In order to consider withdrawal, one would have expected to see a temporary increase in symptom severity. In contrast, the evaluated post-withdrawal period shows an improvement of symptoms, assuming that these might have worsened before. Moreover, both groups differ in the gradual improvement over time in the sleep-related RLS symptoms occurring in the DA group, and possibly, also in RLS symptoms. Therefore, any conclusions comparing both groups is necessarily limited by the small size of the non-DA group.

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Finally, in our view, the data do not exclude a very different interpretation: namely, that some patients in the DA group were indeed undergoing a gradual process of augmentation. Accordingly, following the discontinuation period, both RLS and sleep symptoms would gradually improve over the post-withdrawal period in the DA group (but not in the non-DA group), reflecting a so-called paradoxical response. This would explain two facts that otherwise would remain unclear: First, in the DA-group the time of onset of symptoms occurred early in the afternoon and improved slowly over the entire post-withdrawal period. Second, the same DA group had an abnormally high PLM-index, which did not improve over the entire post-withdrawal period, which may be related to a slower pace of normalization of hypersensitized glutamatergic corticostriatal pathways as suggested by Ferre et al., [17]. Indeed, recent findings suggest that downregulation of adenosine A1 receptor (A1R) in the corticostriatal glutamatergic terminals could result in an increased sensitivity of those terminals to release glutamate, which could be involved in the PLMS symptoms; this could explain the therapeutic effects of dopamine receptor agonists and α2δ-ligands.

Despite these shortcomings, we think that this study opens a new window, and we hope will spark more research into dopaminergic withdrawal in RLS. After all, dopamine withdrawal is well documented in Parkinson's disease, and the only reason to think that it would not occur in RLS because of use of lower doses in RLS than in PD. However, there is some evidence in the literature [15,16] about its existence, and the doses usually used in these patients are indeed sufficient to cause withdrawal upon its discontinuation. Furthermore, when switching from dopaminergic to non-dopaminergic medication in routine daily care, there is a frequent misperception that the latter treatment is, at least initially, less able to control RLS symptoms. We hypothesize that unnoticed DA withdrawal symptoms might be de facto contributing to this false impression.

The debate is open to the reader: there are occasions where data provide more questions than answers, and we believe that this is the case in this situation.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.001.

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