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Editorial

Restless legs syndrome (Willis–Ekbom disease): an urgent need for better treatments

Restless legs syndrome [RLS; also known as Willis–Ekbom disease (WED)] has been under-investigated, under-diagnosed, and poorly treated for a very long time. Although the therapeutic efficacy of levodopa was first acknowledged in the 1980s [1], the use of dopaminergic treatments did not become generalized until after 2005 when three dopamine agonists (ropinirole, pramipexole and lately, rotigotine) were approved for the first-line treatment of RLS/WED in European Union, USA, and Japan. The approval of these drugs by the regulatory agencies was based on numerous large placebo-controlled studies that showed therapeutic efficacy over three to six months [2].

The main long-term consequence of dopaminergic treatment in RLS is augmentation of RLS symptoms. This consists of an increase in symptom severity and intensity, with symptoms starting earlier in the afternoon and expanding to previously unaffected parts of the body. Although augmentation was first described by Earley and Allen in 1996 [3], it was initially thought to be mostly restricted to levodopa. However, over recent years a number of studies have shown that it is also common during treatment with dopamine agonists [4,5], with an approximate yearly incidence rate of seven to eight percent for the oral short-acting agonists pramipexole and ropinirole [2]. Since augmentation is frequently a fluctuating process that tends to worsen over time, the incidence rate increases or accumulates with time, as reported in several retrospective studies [6–8]. These studies show that after a treatment period of approximately 10 years, (the amount of time that has elapsed since the first dopamine agonists were approved), the prevalence of augmentation nears 50% [6–8]. But since RLS is a chronic disease, many patients will need to take treatment for 20 years or more. Due to the approval of most dopamine agonists 10 years ago, data are not available for augmentation occurring with longer use than that. The existing data do not indicate any decrease in the incidence of augmentation with longer duration of use. Thus, it seems likely that when longer follow-up periods become available, prevalence rates will be even higher.

During augmentation, patients on treatment describe symptoms as being similar or even worse compared to before-treatment initiation. For these patients, the period of therapeutic benefit of the dopaminergic drugs was limited. Somehow, the use of the dopamine agonist modifies the pathophysiology of RLS. Drugs that initially alleviated symptoms end up increasing their severity. The reasons could be related to an overstimulation of presynaptic receptors [9].

The introduction of rotigotine, a dopamine agonist acting with a very similar receptor affinity profile to pramipexole and ropinirole, elicited new hopes, mainly due to its different pharmacokinetics and its therapeutic action over the 24-h span [10]. Data for rotigotine are indeed more convincing than for any other dopamine agonist and it is probably the most effective agent within that drug class. Furthermore, initial prospective studies showed lower incidence rates of augmentation than those seen for the shorter-acting agonists. However, in the absence of any direct comparative studies, such retrospective comparisons cannot be made, particularly because of different diagnostic criteria across the various studies [11,12]. Furthermore, all of these prospective studies (not just those performed on rotigotine) based their presumably low incidence rate of augmentation on a fairly restrictive definition of augmentation, termed 'definite' or 'clinically significant augmentation'. In particular, patients with partial symptoms of augmentation were not included in the account. Indeed, as augmentation is a progressive process in which the worsening develops gradually in a fluctuating, progressive way, patients with partial symptoms of augmentation who do not meet full diagnostic criteria should also be considered.

While the prevention of augmentation certainly requires further attention and research, the treatment of acute augmentation constitutes mostly an unexplored area, and very few, low evidence based medicine (EBM)-class studies have been published so far.

A new study, included in this issue [13] performed a one-year observational study on 99 German patients who had suffered from augmentation under oral dopaminergic drugs and were being treated with rotigotine. While on treatment with rotigotine, concomitant RLS medications were used by 57% of the patients. Nevertheless, only 46% of the patients were able to complete the scheduled one-year treatment period with rotigotine. The main reasons for discontinuation from the observational period were adverse events (26%) and lack of efficacy (14%). Among the patients who completed the treatment period, only 37% responded, that is, improved their CGI score by more than 50% (such a definition has been used in the past to define 'responders'). Furthermore, during the 13 months of treatment with rotigotine, 51% of the patients required an additional dose increase during the maintenance phase. An increase in the effective daily dose (once the initial titration period has been completed) usually reflects an increase in symptom severity, and should be considered an early sign of returning augmentation.

In summary, treatment of dopaminergic augmentation with a long-acting dopaminergic drug (such as rotigotine) produced a significant improvement of symptoms in 16% of the patients. Furthermore, in approximately 50% of the patients, early signs of returning augmentation were noted during the first year of treatment. In other words, it seems that long-acting dopamine agonists might be helpful for some patients for a certain amount of time, but after

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a variable initial period of symptom relief, signs and symptoms of augmentation may eventually recur. Thus, it seems reasonable to question the rationale of treating augmentation with dopaminergic drugs that might cause more augmentation.

The problem of augmentation raises numerous questions and provides few answers. It remains a significant clinical problem for at least half of the patients undergoing treatment and represents a failure in therapeutic strategy. As recently as the early 2000s, the main therapeutic challenge in the field of RLS was to develop and deliver treatments to thousands of patients worldwide for which no effective treatment existed. The development and approval of these treatments a few years later caused the erroneous impression that the problem had been definitely solved. It is obvious that such an impression was wrong. Despite being on dopaminergic treatment, many patients today suffer from symptoms that are as severe as they were before the initiation of treatment. Overall, there is a clear need to rethink therapeutic strategies for RLS by focusing efforts on the development of new drugs, preferentially working on non-dopaminergic pathways.

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: http://dx.doi.org/10.1016/j.sleep.2015.12.009.

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