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Guidelines for the first-line treatment of restless legs syndrome/Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation

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SUMMARY

A Task Force was established by the International Restless Legs Syndrome Study Group (IRLSSG) in conjunction with the European Restless Legs Syndrome Study Group (EURLSSG) and the RLS Foundation (RLS-F) to develop evidence-based and consensus-based recommendations for the prevention and treatment of long-term pharmacologic treatment of dopaminergic-induced augmentation in restless legs syndrome/Willis–Ekbom disease (RLS/WED).

The Task Force made the following prevention and treatment recommendations:

As a means to prevent augmentation, medications such as α2δ ligands may be considered for initial RLS/WED treatment; these drugs are effective and have little risk of augmentation. Alternatively, if dopaminergic drugs are elected as initial treatment, then the daily dose should be as low as possible and not exceed that recommended for RLS/WED treatment. However, the physician should be aware that even low dose dopaminergics can cause augmentation. Patients with low iron stores should be given appropriate iron supplementation. Daily treatment by either medication should start only when symptoms have a significant impact on quality of life in terms of frequency and severity; intermittent treatment might be considered in intermediate cases.

Treatment of existing augmentation should be initiated, where possible, with the elimination/correction of extrinsic exacerbating factors (iron levels, antidepressants, antihistamines, etc.). In cases of mild augmentation, dopamine agonist therapy can be continued by dividing or advancing the dose, or increasing the dose if there are breakthrough night-time symptoms. Alternatively, the patient can be switched to an α2δ ligand or rotigotine. For severe augmentation the patient can be switched either to an α2δ ligand or rotigotine, noting that rotigotine may also produce augmentation at higher doses with long-term use. In more severe cases of augmentation an opioid may be considered, bypassing α2δ ligands and rotigotine.

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1. Introduction

Dopaminergic drugs have been widely used over the past decades for the treatment of restless legs syndrome (RLS)/Willis–Ekbom disease (WED), a neurological sensorimotor disorder characterized by an irresistible urge to move the lower limbs especially at rest, and frequently accompanied by nocturnal dysesthesia.

Two decades ago the major problem with RLS/WED management was ensuring that physicians were aware of RLS/WED and able to identify and therefore treat patients with clinically significant symptoms. The first dopaminergic drug to be used for the treatment of RLS/WED was levodopa, and while the first trials were very promising, it soon became apparent that the treatment efficacy of levodopa diminished over time. Of more concern, augmentation, an iatrogenic and at times profound worsening of RLS/WED symptoms following persistent use was recognized [1]. The dopamine agonists ropinirole, pramipexole, and rotigotine, which have longer half-lives than levodopa, were approved for the treatment of RLS/WED between 2004 and 2008 following randomized controlled trials demonstrating their remarkable short-term efficacy for RLS/WED symptoms. However, despite the fact that most patients initially respond very well to dopamine agonists and that this class of drugs is generally well tolerated over the short-term, longer studies and clinical experience have demonstrated that treatment efficacy diminishes in many patients over time, and/or augmentation develops, albeit after a longer duration of treatment than with levodopa [2]. A recent US community-based study estimated that 76% of all patients treated with dopaminergic agents required either a dose increase and/or showed indications for partial or full augmentation, with a yearly incidence rate of approximately 8% [3].

Therefore, today, a major issue with RLS/WED concerns managing treatment over the long-term, and in particular preventing and treating augmentation, which has become a common and increasing challenge that hinders the successful long-term treatment of RLS/WED with dopamine agonists.

There are presently no official augmentation treatment guidelines, and this situation is particularly troublesome for primary care physicians and specialists without expertise in RLS/WED management. Currently, physicians find themselves in a situation similar to the early 1990s, not knowing how to optimally manage RLS/WED patients over the long-term. For this reason, the International RLS Study Group (IRLSSG, http://www.irlssg.org) appointed a Task Force together with the European RLS Study Group (EURLSSG, http://www.eurlssg.org) and the RLS Foundation (http://www.rls.org) to review the current evidence and reach a consensus on the prevention and treatment of RLS/WED augmentation.

2. Process and objectives

2.1. Task force

The Executive Committee of the IRLSSG, together with the EURLSSG and the RLS Foundation, established an international Task Force to develop recommendations for the prevention and treatment of RLS/WED augmentation. The 13 members of the Task Force (authors of the current recommendations) include neurologists, psychiatrists, pulmonologists, sleep specialists and pharmacologists from the USA, Europe and Japan, all with extensive experience in RLS/WED treatment. All members completed the IRLSSG conflict of interest statement (Appendix 1).

2.2. Objectives

The objectives of the Task Force were (1) to review the evidence on the prevalence, identification, prevention, and treatment of augmentation and, given the paucity of these data, to (2) complement these with consensus-based recommendations of RLS/WED experts.

3. Methods

3.1. Literature and search strategy

Published papers (meta-analysis, randomized trials, cohort studies, case–control studies, observational studies) were identified from the following sources published before 2 October 2014: Cochrane Database of Systematic Reviews (CSDR) in the Cochrane Library, Database of Abstract of Reviews of Effects (DARE) in the Cochrane Library, CENTRAL (Cochrane Central Register of Controlled Trial) in the Cochrane Library, National Library of Medicine's MEDLINE database, EMBASE database, and CINAHL database. The electronic databases were consulted using the following search terms: {[(restless* OR jitter* OR anxiety*) AND (limb* OR leg* OR tibia*) OR ekbom* OR "restless legs syndrome" OR "willis ekbom disease")] AND treat*}.

The search strategy identified 2718 references (including possible duplicates). A further search with MeSH terms {("Restless Legs Syndrome"[Mesh]) AND ("Clinical Trials as Topic"[Mesh] OR "Therapeutics"[Mesh])} identified 538 references (including possible duplicates).

Inclusion criteria were articles in any language with mean patient follow-up > 6 months with any assessment of augmentation (clinical impression, NIH/MPI criteria), as well as any articles which attempted to identify the characteristics of augmentation (clinical identifiers, neurophysiological predictors). After assessing from title, abstract or full text of articles, a total of 45 articles for RLS/WED were eligible for inclusion in the review (Table 1).

3.2. Outcome measures

Table 1 shows the tools that were used to identify and assess augmentation.

3.3. Data extraction and evaluation of the evidence

Studies were divided into one of the following seven categories: (1) identifying augmentation, (2) controlled trials with a duration between six and 12 months, and (3) more than 12 months, (4) uncontrolled open-label, case series with a duration between six and 12 months, and (5) more than 12 months, (6) treatment of augmentation, and (7) treatment withdrawal.

3.4. Consensus-based clinical recommendations

Consensus was defined by at least 90% of the task force agreeing on a clinical recommendation. All task force members agree with the current recommendations.

3.5. Approval of treatment recommendations

Summaries of both the recommendations were prepared and first presented at the annual meeting of the IRLSSG on March 21, 2015, in Seoul, South Korea. In addition, an e-mail was sent to all IRLSSG and EURLSSG members as well as to the Medical Advisory Board of the RLS Foundation with a copy of the recommendations. Members were given an opportunity to comment on the recommendations from March 21 to May 11, 2015. The Executive Committee of the IRLSSG approved the final recommendations on May 12, 2015.