Sleep Medicine 14 (2013) 675–684

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Special Section in Sleep Medicine

The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group

Diego Garcia-Borreguero [a,*], Ralf Kohnen [b,c], Michael H. Silber [d,e], John W. Winkelman [f,g], Christopher J. Earley [h,i], Birgit Högl [j], Mauro Manconi [k], Jacques Montplaisir [l], Yuichi Inoue [m,n], Richard P. Allen [h,i,1]

[a] Sleep Research Institute, Madrid, Spain
[b] Research Pharmaceutical Services Inc., Fort Washington, PA, United States
[c] Department of Psychology, University of Erlangen-Nuremberg, Nuremberg, Germany
[d] Mayo Clinic College of Medicine, Rochester, MN, United States
[e] Center for Sleep Medicine and Department of Neurology, Mayo Clinic, Rochester, MN, United States
[f] Harvard Medical School, Boston, MA, United States
[g] Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States
[h] Department of Neurology, Johns Hopkins University, Baltimore, MD, United States
[i] Sleep Disorders Center, Johns Hopkins Bayview Medical Center, Baltimore, MD, United States
[j] Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
[k] Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital, Lugano, Switzerland
[l] Departments of Psychiatry and Neuroscience, Université de Montréal, Montreal, Canada
[m] Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan
[n] Department of Somnology, Tokyo Medical University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 25 January 2013
Received in revised form 29 May 2013
Accepted 31 May 2013

Keywords:
Restless legs syndrome
Willis–Ekbom disease
Pharmacologic therapy
Periodic limb movements of sleep
Calcium channel alpha 2 delta ligands
Opioids
Hypnotics and sedatives
Dopamine agents

ABSTRACT

A Task Force was established by the International Restless Legs Syndrome Study Group (IRLSSG) to develop evidence-based and consensus-based recommendations for the long-term pharmacologic treatment of restless legs syndrome/Willis–Ekbom disease (RLS/WED). The Task Force reviewed the results of all studies of RLS/WED treatments with durations of 6 months or longer presented at meetings over the past 2 years, posted on Web sites of pharmaceutical companies, or published in peer-reviewed journals, asking the questions, "What is the efficacy of this treatment in patients with RLS/WED?" and "What is the safety of this treatment in patients with RLS/WED?"

The Task Force developed guidelines based on their review of 61 papers meeting inclusion criteria, and using a modified evidence-grading scheme. Pregabalin has been established as effective for up to 1 year in treating RLS/WED (Level A evidence). Pramipexole, ropinirole, and rotigotine have been established as effective for up to 6 months in treating RLS/WED (Level A). The following drugs have been established as probably effective (Level B) in treating RLS/WED for durations ranging from 1 to 5 years: gabapentin enacarbil, pramipexole, and ropinirole (1 year); levodopa (2 years); and rotigotine (5 years). Because of associated safety concerns, pergolide and cabergoline should not be used in the treatment of RLS/WED unless the benefits clearly outweigh the risks. Other pharmacologic therapies have insufficient evidence to support their long-term use in treating RLS/WED.

The IRLSSG Task Force also developed consensus-based strategies for the prevention and treatment of complications (such as augmentation, loss of efficacy, excessive daytime sleepiness, and impulse control disorders) that may develop with the long-term pharmacologic treatment of RLS/WED. The use of either a dopamine-receptor agonist or $\alpha_2\delta$ calcium-channel ligand is recommended as the first-line treatment of RLS/WED for most patients, with the choice of agent dependent on the patient's severity of RLS/WED symptoms, cognitive status, history, and comorbid conditions.

* Corresponding author. Address: Sleep Research Institute, Alberto Alcocer 19, 28036 Madrid, Spain. Tel.: +34 913454129; fax: +34 913509095.
E-mail address: dgb@iis.es (D. Garcia-Borreguero).

[1] On behalf of the International Restless Legs Syndrome Study Group (www.irlssg.org).

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http://dx.doi.org/10.1016/j.sleep.2013.05.016

1. Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease (WED), is a commonly occurring neurologic disorder characterized by an irresistible urge to move the legs, usually accompanied by dysesthesias that are relieved by movement, exacerbated by rest, and worse in the evening and night [1]. Sleep and quality of life can be severely affected [2–5].

RLS/WED was largely unrecognized until the 1990s when studies documenting its clinical relevance were conducted and significant epidemiologic studies revealed RLS/WED to be a notable public health concern [6]. To date, evidence-based treatment guidelines [7–13] have been primarily based on studies lasting no longer than 12 weeks, whereas RLS/WED quite often is a lifelong disease [14]. Long-term clinical experience with the treatment of patients with RLS/WED has revealed both the significance of problems that arise during the short term (e.g., weight gain, impulse control disorders [ICDs], mood disturbances) and the emergence of new problems during long-term treatment (e.g., augmentation, loss of efficacy). Thus the current evidenced-based guidelines do not suffice for providing clinical guidance for the long-term treatment of RLS/WED.

2. Process and objectives

2.1. Task Force

The Executive Committee of the International RLS Study Group (IRLSSG) established an international Task Force to develop recommendations for the long-term treatment of RLS/WED. The members of the Task Force completed the IRLSSG conflict of interest statement (Appendix–Conflict of interest disclosures). Financial support for this endeavor was requested from all pharmaceutical companies involved in the treatment of RLS/WED; funding was ultimately provided by unrestricted education grants from Xenoport and UCB Pharma. Funders did not participate in the development of these guidelines and recommendations, and they were not privy to this document before publication.

2.2. Objectives

The objectives of the Task Force were (1) to develop evidence-based guidelines for the efficacy and safety of pharmacologic agents for the long-term treatment of RLS/WED and (2) given the limitations of current data, to complement these with consensus-based recommendations of experts regarding the long-term treatment of RLS/WED and management of common complications that may arise.

3. Methods

3.1. Literature search and strategy

Databases that were searched included MedLINE, CINAHL, clinicaltrials.gov, abstracts from key 2010 and 2011 meetings, and drug company Web sites using the freeform search term of *restless legs syndrome* in combination with each of the following terms: *treatment*, *therapy*, and *drugs* and the MeSH term *restless legs syndrome*, *therapeutics*. Inclusion criteria were any pharmacologic treatment of adults with RLS/WED, with the results published in any language over any timeframe and with a study duration of a minimum of 6 months. A review of the literature search strategy is detailed in the Appendix (Detailed literature search and data extraction).

3.2. Outcome measures

An overview of the primary tools used in RLS/WED trials to measure the efficacy of long-term pharmacologic treatments is provided in Table 1.

3.3. Data extraction and evaluation of the evidence

Evidence was graded based on Agency for Healthcare Research and Quality [15] and European Federation of Neurological Societies [16] systems, which were then adapted to support the evaluation of long-term treatment studies. Developing long-term treatment guidelines is complicated both by the limited number of studies of sufficient duration (i.e., $\geqslant$6 months) and also by the need to adjust evidence criteria, taking into account the types of studies appropriate to convincingly document evidence of long-term treatments. In particular, obtaining data on efficacy for treatments of 1–10 years or longer generally would require retrospective or planned prospective case series. When these studies were performed well and met the criteria for Class III evidence except that they were prospective open-label studies or case series and not controlled trials, it was felt that they provided useful information for making a recommendation. Therefore, two subcategories were added to Class III (Tables 2 and 3) for prospective open-label studies and for prospective and retrospective case series without control groups (henceforth, the original Class III is denoted as Class $\text{IIIa}_{\text{IRLSSG}}$; the prospective open-label studies as Class $\text{IIIb}_{\text{IRLSSG}}$; and the prospective and retrospective case series without control groups as Class $\text{IIIc}_{\text{IRLSSG}}$). We felt that this was in line with the intention of the original Class III when applied to long-term studies. Data extraction is described in the online Appendix (Detailed literature search and data extraction).

3.4. Consensus-based clinical recommendations

Consensus was defined by at least 80% of the members of the Task Force agreeing on a clinical recommendation.

3.5. Approval of treatment recommendations

Summaries of both the evidenced-based and the consensus-based treatment recommendations were prepared and presented at the annual meeting of the IRLSSG on June 9, 2012, in Boston, Massachusetts. In addition, an e-mail was sent to all IRLSSG members with a link to an online copy of the recommendations. Members were given an opportunity to comment on the recommendations from June 9 to June 24, 2012. The Executive Committee of the IRLSSG approved the final recommendations on July 17, 2012.

4. Evidence-based guidelines for the long-term pharmacologic treatment of RLS/WED

Sixteen pharmacologic agents have been studied for the treatment of RLS/WED for at least 6 months. The following sections review the evidence and provide evidenced-based recommendations for each drug. The evidence discussed below is presented by study in the online Appendix (Table A1); a summary of the final evidenced-based recommendations is provided in Table 4.

4.1. Dopaminergic agents

4.1.1. Non-ergot-derived dopamine-receptor agonists

4.1.1.1. Pramipexole. double-blind 26-week study [17] (Class I) randomly assigned 331 patients with idiopathic RLS/WED to