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Sleep disorders in neurology

French consensus: Treatment of newly diagnosed restless legs syndrome

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INFO ARTICLE

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ABSTRACT

Treatment of restless legs syndrome (RLS) must only be considered after a definite positive diagnosis. The RLS phenotype must be characterised precisely, iron deficiency always tested for, and aggravating factors eliminated when possible. Medical treatment is considered for severe or very severe forms and based on dopaminergic agonists, α2δ-1 ligands and/or opioids. First line treatment will be a low-dose monotherapy and the choice of treatment depends on the results of the clinical examination and investigations.

1. Abbreviations

DA	dopaminergic agonists
MA	market authorisation
IRLS	International Restless Legs Syndrome Study Group rating scale
IRLSSG	International Restless Legs Syndrome Study Group
PLM	periodic limb movements
PLMS	periodic leg movements of sleep
RLS QoL	Restless Legs Syndrome Quality of Life
SF-36	Short Form - 36
RLS	restless legs syndrome

2. Introduction

Before considering initiating a medical treatment it is necessary to:

- establish a positive diagnosis of restless legs syndrome (RLS);
- explain the disease and its physiopathology to the patient;
- look for factors that aggravate RLS;
- evaluate the severity of the RLS. It should be emphasised that the majority of research has evaluated the effectiveness

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of treatments on moderate to severe forms (IRLS > 10) based on the international restless legs syndrome rating scale (IRLSSG) score. In clinical practice, the impact on patients' quality of life (sleep, social life, mood) must be factored into the choice of treatment. The severity scale covers these aspects but they should always be discussed with the patient before any therapeutic decision is made.

These 3 stages are detailed in the RLS diagnosis article. It is also necessary to:

- discontinue, if possible, all aggravating treatments: antidepressants (from all classes), antipsychotics, lithium, antihistamines, and sodium oxybate;
- provide the patient with healthy lifestyle guidelines regardless of the severity of the RLS (Box 1). These will enable RLS symptomatology to be minimised. These guidelines are based both on the literature and the experience of our expert group.

3. Treatment of a potential iron deficiency

Iron status must always be checked before initiating a medical treatment. The majority of research has evaluated the effect of iron supplementation for ferritin < 50 μg/mL. Some patients benefit from iron supplementation with ferritin < 75 μg/mL. The effectiveness of iron supplementation in RLS has been recognised for a long time. The cause of the iron deficiency should also be sought and treated. We recommend first line oral supplementation with ferritin levels tested after 3 months. If *per os* iron supplementation is ineffective the intravenous route can be considered as an alternative. The choice of intravenous iron depends on the physicians' experience and the availability of intravenous iron products in the hospital. Intravenous iron treatment should be given in hospital because of the risk of anaphylactic shock. There is less of a risk with the ferric carboxymaltose based formula which is the only one to have proven higher efficacy than placebo in double-blind randomised studies [1,2], (using iron perfusions with a maximum dosage of 1000 mg in one go). Ferritin must be checked 4 to 6 weeks after the perfusion.

Box 1. Healthy lifestyle guidelines for RLS.

- Regular sleep-wake times
- Relax before going to sleep
- Avoid screen use before going to sleep
- Do not sleep in a room that is too hot
- No physical activity during the evening
- Avoid alcohol (especially white wine and champagne), coffee, nicotine
- Go to bed earlier to avoid the symptoms when falling asleep (when possible)
- Suggest exacting intellectual activity when symptoms are troublesome (for example, a watchmaker is never bothered by RLS when concentrated on his work)

3.1. *Specific cases*

Intravenous supplementation can be given as a first line treatment to patients with a very serious form of RLS associated with low ferritin levels. Depending on the clinical context (e.g. an elderly subject), a cause of the iron deficiency should be sought: e.g. a Hemoccult test to test for a digestive source for the iron deficiency.

Oral supplementation should be preferred for children. Good tolerance of the treatment is a priority, and the physician should check for digestive pain, cramps or changes in intestinal transit. Children generally start on 1–3 teaspoons a day (34–102 mg/d) of Ferrostrane® since it has the least effect on digestive transit and because the dose can be adjusted easily. If this treatment causes digestive problems 66 mg Fumafer® coated pills can be proposed or, for those who cannot swallow pills, Fumafer® in powder (1–3 spoons-dose/day, 33–99 mg/d) or Timoferol® 50 mg capsules (as the capsule can be opened). In the event of digestive intolerance an intravenous perfusion of iron can be used as second line treatment.

For patients with severe or very severe RLS without iron deficiency, or when iron supplementation has been ineffective, medical treatment should be considered. Three categories of medication are available: dopaminergic agents, certain anti-epileptics and opioids.

4. Dopaminergic agents

Dopaminergic agents consist of levodopa and dopaminergic agonists. Only 3 molecules are licensed for use on the French market: Adartrel®, Sifrol® and Neupro®. None are currently reimbursed for restless legs syndrome.

4.1. *Levodopa*

Several placebo-controlled randomised studies have proved the effectiveness of levodopa in treating RLS. Due to the risk of excessive self-medication and developing augmentation syndrome, we do not recommend the use of this treatment for RLS.

4.2. *Dopaminergic agonists*

Dopaminergic agonists can be divided into two categories: ergot-derivatives and non-ergot derivatives.

Ergot-derivatives are not recommended for RLS due to side effects: risk of fibrosis (hepatic, pulmonary, pericardial and retroperitoneal) and cardiac valvulopathy.

Non-ergot-derivative dopaminergic agonists available in France and indicated for RLS are Adartrel®, Sifrol® and Neupro®. The large number of high quality scientific articles has resulted in their use as first line treatment of moderate to very severe forms of RLS for over 10 years.

4.2.1. *Pramipexole (Sifrol®)*

Pramipexole is a D1, D2 and D3 agonist of dopaminergic receptors, with higher affinity for D3 receptors. Its half-life is 8–12 hours and time to onset of action between 1 and

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