Author's response to reviews

Title: Algorithms for the diagnosis and treatment of restless legs syndrome in primary care

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Author's response to reviews: see over
Dear Professor Korczyn,

We thank you for considering our paper for publication and for the peer reviews by Helio Teive and Richard Allen. We answer the reviewer’s comments below.

Sincerely,

Diego Garcia-Borreguero

Reviewer: Helio Teive

Reviewer’s report:
This is a well-written and very nice review paper about restless legs syndrome (algorithms for the diagnosis and treatment in primary care).
I have only one comment to the authors.
When they discuss the differential diagnosis and mimics (table 3), particularly about peripheral neuropathy, the authors could mention the classical and seminal description of professor Ekbom (Ekbom KA. Asthenia Crurum Paraesthetica “Irritable legs”. Acta Medica Scandinavica, 1944, page 198): “The paraesthesia is felt in the lower legs (not the feet). It is never experienced superficially in the skin, but deep down in the calf or sometimes the shin).
**Answer**: Thank you for your review and your suggestion. We have made the change that you requested.

**Reviewer**: Richard Allen  
**Reviewer’s report:**  
This is a much-needed paper to help advance better identification and treatment of RLS. There are some problems that you should consider. Some of these are careless and others represent a lack of critical thought that dampens enthusiasm for the manuscript.

These are all major compulsory revision requests  
1) In the introduction, point a, the reference for 50% with sleep less than 5 hours is very poor study using a simple questionnaire to identify RLS patients that had at its best 50% positive predictive value. There are now studies with physician diagnosed RLS that show this estimate is far too extreme. Those with physician judged medically significant RLS have an average self-reported sleep time of about 5.2-5.4 hours and milder RLS has sleep times of about 6.5 hours (Allen, Sleep Med, 2010).  

The 5-hour statement here is an example of exaggeration that produces skepticism about the real significance of RLS. Even some of the PSG data with moderately severe clinical cases of RLS show higher sleep times (e.g. Saletu, 326 mins). You should either reference better studies with a more honest statement about the sleep loss or be more vague. Hopefully you have been careful not to exaggerate your case too much. You don’t need to do that, but when you do such as this effort to cherry pick to make an incorrect point you lose credibility before anyone bothers to read the rest of the paper. In this regard the issue of daytime drowsiness is not well documented except in some mild RLS patients, so if you emphasize this and the clinician is looking at his patient who despite reporting significant sleep loss is conspicuously alert in the office the clinician will start to doubt the patient’s report of poor sleep. Precision and accuracy is very important.

**Answer**: We agree with the reviewer on the importance of precision and accuracy for the progress of any science. Also, we agree that exaggeration of the burden of disease can contribute to reducing the credibility of the clinical burden related to RLS among the medical
community. Having said that, we believe that there is no exaggeration in our statement. The impact of RLS on quality of life, and on sleep in particular, depends heavily on the degree of severity of RLS that is investigated. However, for most studies investigating moderate to severe RLS, the average sleep time is around 5 hrs time. We had cited Kushida’s paper with less than 5 hrs of sleep in 50% of the sample (not in all!). The reviewer mentioned his own paper, e-published after our paper had been written and submitted, which provides a slightly higher sleep time (5.2-5.4 hrs/day, not very different from Kushida’s results). Other studies not cited by the reviewer (Baos, 2009; O’Keeffe) provide a daily sleep time of approx 5 hours and lead us to believe that if there was any exaggeration this was certainly not ours.

For the purpose of conciliation in this artificial controversy, we have changed our statement to:
In several large surveys, most RLS patients slept an average of 5 hours a day.

Regarding, the mention of drowsiness, unlike daytime sleepiness we agree that it has not been properly evaluated. It is likely that a significant part of the RLS population (not necessarily the milder ones, suffer form drowsiness during asymptomatic periods in the morning. However, no adequate studies (both size wise and methodologically) have been performed so far.

2) You are inconsistent on what you report as the range of lifetime prevalence of RLS…. 3 – 10% in the abstract and 5 – 10% in the introduction. This is confusing to readers, better to be consistent. 3 – 10% is probably more accurate.

Answer: OK

3) In discussing the underdiagnosis you ignore the problem of the questionnaire approach with about a 50% false positive identification. The underdiagnosis may represent an artifact of too many in these studies who do not have RLS or have only such mild RLS that diagnosis makes no sense. How do you know that the doctors were not right rather than your questionnaires. There is one study with physician diagnosis that you do not even reference. I am bothered by the lack of critical thought with this part of the manuscript, especially if you are striving for credibility. This needs to be rewritten. As written it has limited credibility.
**Answer:** To illustrate the fact that RLS is underdiagnosed, we are adding a reference on which the reviewer is one of the authors. It clearly states in that: "... Clinically significant RLS is common (prevalence, 2.7%), is underdiagnosed, and significantly affects sleep and quality of life.” Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165(11):1286-92.

4) The estimate of 35 – 66% of RLS as having moderate to severe disease is certainly unlikely and again would cause readers to wonder why their clinical experience differs from this. This might be true if you talk about only those with symptoms twice a week or more, but the 66% figure again seems likely to represent problems with the questionnaiare data approach. This could be removed. The physician diagnosed RLS had a population prevalence of less than 1% for clearly medically significant RLS and less than 3% for severe to moderate medical significance. These are likley to be more realistic estimates – and reflect considerably less than expected from your presentation here. Telling doctors that they are missing so many patients creates a disconnect with their clinical experience and is likely to turn them off, especially when it is probably much exagerrated here. Again take a look at the results of the physician diagnosed study.

**Answer:** This has been removed.

5) The argument for not using the algorithm from the MAYO clinic publication seems a bit weak. It Is not clear the European guidelines should differ from American ones. The added data is helpful and newer treatment opitons need to be considered. I wonder if this should be reworded to emphasize the newer treatment options.

**Answer:** Reference to the MAYO publication not addressing a European audience has been removed. However, the reviewer should be reminded that The Mayo clinic algorithm was exclusively written by American authors, and reflected American but not European standards of
diagnosis (i.e., minimal or non-existent role for polysomnography) and treatments (it does not even mention well-studied drugs like cabergoline.

6) You have misstated the first diagnostic criteria.
It is an urge to move USUALLY accompanied or caused by ... You left out this important usuauully ... but state it correctly below the criteria
The urge or sensations BEGIN or worsen with rest... and not as you state increase or worsen with rest the begin with rest is a critical concept.
The symptoms become worse in the evening or night, not as you state in the night. The night is too restrictive and not accurate.
Answer: This has been changed.

7) The high rate of RLS with PD may reflect the medicaiton effect more than problems with diagnosis, I am not certain that it is correct to suggest that the experienced clinician such as Ondo who reports somewhat high rate of RLS with PD would not make an accurate differential diagnosis.
Answer: This has been changed to: The high prevalence of concomitant RLS in the Parkinson’s disease population may reflect the medication effect, however there may also bemimics or overlap of some PD symptoms with RLS.

8) Statements like “many physicians are unaware that …. doses required” should be avoided without any supporting evidence. There is no need to talk about physician ignorance if that is the group you want to influence and certainly not good to be so critical here.
Answer to Richard Allen: This has been changed to:
It is important that physicians know that for the dopaminergic agents the doses required for RLS are far lower than those used to treat Parkinson’s disease patients.

9) There is a very awkward sentence “Treatment for RLS should only be initiated when the symptoms impair the patient’s quality of life, daytime functioning, social functioning or sleep to be impaired.” Please clean this up

Answer to Richard Allen: This has been changed to:
RLS should only be treated when it is clinically significant, that is, when symptoms impair the
patient’s quality of life, daytime functioning, social functioning or sleep.

10) I went to the web site to see the recommended diary and could not find it there. It certainly is not easy to find if it is there at all. Please correct this problem

**Answer:** The link appears in the menu on the home page and is also referred to in the main text, nevertheless we have addressed this and have made the entire menu more visible.

11) For intermittent treatment would you not also consider a GABA active hypnotic if it mostly disturbs sleep.

**Answer:** Yes

12) When evaluating iron status from blood samples the transferrin measure is expensive and not very helpful. I wonder if they meant this to be transferrin saturation.

**Answer to Richard Allen:** Yes.

13) What is meant by the phrase “Frequently intravenous iron therapy is necessary.” What makes this necessary???

**Answer:** This has been changed to:

“In some cases, intravenous iron therapy is can be an effective treatment.”

14) The phrase “simultaneously to symptomatic treatment” is confusing presumably this was meant to say concurrent with other treatments….

**Answer:** This has been changed.

15) Why painful forms of RLS …. “should” be treated with alpha-2 drugs. This is a strong statement. What about opioids? In some cases the dopaminergic drug may also work.

**Answer:** This has been changed to

"might respond well to"

16) The recommendation of follow up every 6 months seems a bit extreme. Yearly follow up is likely to work better, but there are certainly no basis for
making this rather strong statement about follow up every 6 months. This will be difficult for many primary care doctors. Could this be more flexible? I worry it feels you are out of contact with the scheduling demands in primary care.

**Answer:** This now reads 6-12 months.

17) Why is the RLS diagnostic index included without any reference to its use or data supporting its utility? It is unlikely primary care doctors will use this sort of scale or interview process. This will take much too long for most doctors. I have trouble imagining it ever being used in primary care setting.

**Answer:** We have added the reference: Benes H, Kohnen R. Validation of an algorithm for the diagnosis of Restless Legs Syndrome: The Restless Legs Syndrome-Diagnostic Index (RLS-DI). Sleep Med 2009;10:515-523.

18) The recommended laboratory evaluation differs in the table from that described for iron status in the text. Serum iron may not be very helpful and the critical criteria for ferritin should be consistent.

**Answer:** OK