Author's response to reviews

Title: Use of near-infrared light to reduce symptoms associated with Restless Legs Syndrome: a case report

Authors:

Ulrike H Mitchell (rike_mitchell@byu.edu)

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Author's response to reviews: see over
Enclosed is the submitted revision of my case report, titled “Use of near-infrared light to reduce symptoms associated with Restless Legs Syndrome: a case report” for your consideration. This is the first case report showing evidence that infrared light therapy could become a new drug-free treatment option for patients suffering from this neuro-sensory disease – an important piece of information for about 10% of the American population.

The changes I made in the manuscript are in red. Please also see my letter (below) to the reviewers where I address their comments.

Thank you for your time and consideration; I look forward hearing from you.

Sincerely,

Ulrike H. Mitchell
Dear Reviewers,

Thank you for reviewing my submission entitled: “use of near-infrared light to reduce symptoms associated with Restless Legs Syndrome: a case report”. I have used your valuable comments to make the manuscript better. One reviewer suggested shortening the report; I was not able to do that – I actually lengthened it quite a bit following your suggestions. In detail, the following was changed (all changes are in red in the uploaded paper):

I took the word “I” out of the paper and changed the wording to a passive voice.

I added that the patient gave written informed consent to take part in the trial. Since the case report was part of a RCT (this patient was my first participant in the RCT), I was asked to reference the trial. It is not registered, since Brigham Young University is not affiliated with any of the registries and it has not been published; therefore I cannot reference it.

I was also asked to add a author’s contribution section. As the sole author I was responsible for conceiving the idea, performing the treatments, collecting the data, analyzing the data and writing the report.

**Introduction:** a more up-to-date description of the treatment options for RLS was added: The pathophysiology of RS is not fully clear. RLS can be classified into primary or secondary forms, delineating genetic and idiopathic contributions or involvement of other underlying pathologies respectively. Secondary RLS is usually dealt with by treating the underlying causes or associated medical conditions. For primary RLS dopaminergic medications are considered first line treatment for their effectiveness and usual rapid and dramatic improvement of the symptoms [6]. Other drugs, such as opioids (methadone, hydrocodone), GABA analogue (gabapentin,
pregabalin), and benzodiazepines (clonazepam) are also used to treat moderate to severe RLS [6, 7].

**Case Presentation:** The three diagnostic supportive features were added (and referred to later – i.e. the patient’s two daughter have RLS, no PLM and the patient’s non-responsiveness to dopaminergic treatment,): The IRLSSG also defined three supportive features. While they are not essential to the diagnosis of RLS, their presence can help resolve diagnostic uncertainty; they are: family history, presence of periodic limb movement and the response to dopaminergic treatment [3].

More detailed information on the patient’s medication intake was given, (such as dose and kind of sleeping pills she was taking), “muscle relaxant” was changed to “benzodiazepine” and more information about the dosage of fluoxetine was obtained.

**Discussion:** I added more information on the placebo effect in RLS: A recent meta-analysis [27] assessing the placebo effect in RLS treatment studies found a substantial placebo response associated with RLS treatment. This response was greater for the IRLS compared to other scales, possibly related to its multidimensional assessment character. On average, more than one-third of RLS subjects experienced a major improvement of RLS symptoms while receiving placebo treatment. The authors propose that the reason for this might be related to RLS’ unique responsiveness to dopaminergic agents and opioids – both systems implicated in the placebo response. The question of whether this patient’s improvement was likely due to a pure placebo effect can only be answered by conducting a randomized controlled trial.
I also added a whole paragraph on the possible mechanism behind the NIR treatment and its implications on RLS: The pathophysiology of RLS is not clear. In the 1940s and 1950s it was hypothesized that decreased blood flow was responsible for the symptoms associated with RLS [16]. Ekbom [2] believed that vasodilators given to RLS sufferers would decrease the symptoms. Today it is widely accepted that the CNS is involved in RLS, but the original hypothesis of a vascular association still exists. One study reports that increased vascular blood flow with enhanced external counter pulsation significantly decreased RLS symptoms in six patients [16]. Another study [17] showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder. The author of this case report theorizes that the symptoms associated with RLS could stem from a feedback mechanism where decreased tissue perfusion in the legs signals to the brain the need to move. Activity, such as movement or walking, increases blood flow to the muscle and tissue [18]. The proposed mechanism of NIR therapy is its ability to generate NO in the endothelium [19] and even in the lumen directly by dissociating NO from hemoglobin contained in erythrocytes [14, 20]. Nitric oxide is able to initiate and sustain vasodilation [21, 22] and, as a neurotransmitter itself, has influence on neurotransmission. [22] Phototherapy, which includes NIR, has been known to decrease pain by changing cell membrane permeability. This leads to enhanced synthesis of endorphins, increased nerve cell potential and hence to pain relief [23]. NIR consequently can affect three factors associated with RLS: vasodilation [16], neurotransmission [24] and pain relief [25]. It is thus conceivable that NIR could positively impact this pathology. Recent findings could validate this hypothesis as well as function as the missing link between theory and fact. A German study [26] discovered significant evidence for an association of RLS with sequence variations in the NOS1 gene,
pointing to a possible involvement of the NO/arginine pathway in RLS disease susceptibility and in the etiology of RLS.

I want to thank everybody involved in reading our paper and making excellent suggestions. I hope that the paper is now better and stronger and suitable for publication.

Thank you,

Ulrike Mitchell