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CLINICAL REVIEW

The influence of antidepressants on restless legs syndrome and periodic limb movements: A systematic review

Bhanu Prakash Kolla [a, b, *], Meghna P. Mansukhani [b], J. Michael Bostwick [a]

[a] Department of Psychiatry & Psychology, Rochester, MN, USA
[b] Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

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SUMMARY

Restless legs syndrome is commonly co-morbid with medical conditions that are treated with antidepressant medications, such as depression, anxiety, fibromyalgia, and chronic insomnia disorder. Evidence from case reports and cross-sectional studies suggests that antidepressants may induce or worsen restless legs syndrome and increase periodic limb movements. We undertook a systematic review of the literature to identify and collate all prospective studies that measured restless legs syndrome symptoms and/or periodic limb movements following the introduction of an antidepressant. Eighteen studies were eligible for inclusion. Current data indicate that onset or exacerbation of restless legs syndrome and rise in frequency of periodic limb movements are uncommon following the initiation of an antidepressant. Among the various antidepressants, mirtazapine may be associated with higher rates of restless legs syndrome and periodic limb movements. One small study of normal volunteers suggested that venlafaxine may be associated with an increase in restless legs syndrome symptoms and periodic limb movements. Sertraline, fluoxetine, and amitriptyline appear to increase periodic limb movements that do not disrupt sleep and are thus unlikely to be clinically significant. On the other hand, bupropion may reduce restless legs syndrome symptoms, at least in the short term. Sedating antidepressants such as trazodone, nefazodone, and doxepin do not seem to aggravate periodic limb movements. The current evidence is limited by poor study design, inadequate use of standardized questionnaires, and heterogeneous populations studied for variable lengths of time. Future research should attempt to remedy these shortcomings.

Introduction

Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is characterized by discomfort in the limbs associated with an urge to move the limbs, temporary improvement with movement, and worsening symptoms at rest and in the evening [1]. About 70% of patients with RLS/WED have periodic limb movements (PLMs) of sleep [2]. RLS/WED affects about 2.1%–5% of the general population [3], however, increased rates have been described in patients with depressive disorders, anxiety disorders, and fibromyalgia [4,5], medical conditions that are frequently treated with antidepressant (AD) medications. A study of patients presenting to a psychiatric clinic with unipolar depression reported rates of RLS/WED as high as 27% [6]. Conversely, patients with RLS/WED report high rates of depressive disorders [7]. Sedating AD are also used in the treatment of insomnia, which in turn may be a consequence of untreated RLS/WED and PLMs [2].

Some cross-sectional studies and case reports suggest that AD use is associated with the onset or worsening of RLS/WED symptoms [8–13] and higher rates of PLMs [14]. In the largest cross-sectional study of 18,980 subjects examining this association, the use of selective serotonin reuptake inhibitors (SSRI) medications was significantly associated with RLS/WED [15]. The American Academy of Sleep Medicine practice parameters on the treatment of RLS/WED and PLMs in adults published in 2012 made no specific recommendation with regard to the avoidance of AD due to conflicting evidence [16]. On the other hand, the International Restless Legs Syndrome Study Group (IRLSSG) guidelines in 2013 recommended asking patients with RLS/WED about the use of AD as part of the evaluation for earlier onset or increase in severity of symptoms [17].

* Corresponding author. B.P. Kolla, MD MRCPsych, Center for Sleep Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Fax: +1 507 266 7772.
E-mail address: kolla.bhanuprakash@mayo.edu (B.P. Kolla).

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Abbreviations

A	adaptation
AD	antidepressant
IRLSSG	International Restless Legs Syndrome Study Group
P	placebo
PLM	periodic limb movements
PLMAI	periodic limb movement arousal index
PLMI	periodic limb movement index
PSG	polysomnogram
RCT	randomized controlled trial
RLS/WED	restless legs syndrome/Willis-Ekbom disease
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitors
T	trazodone

It is unclear at this time whether all AD carry the same risk of increasing RLS/WED and PLMs. If prospective studies demonstrate that AD significantly influence the risk of RLS/WED and PLMs, this may have an important impact on treatment decisions in clinical practice, as RLS/WED frequently co-occurs with depression, anxiety, pain, and insomnia.

To examine the relationship between the use of AD and RLS/WED symptoms as well as PLMs, we performed a systematic review of the literature to identify studies that measured RLS/WED symptoms or PLMs in patients receiving these medications. We limited the review to studies that prospectively measured RLS/WED symptoms and/or PLMs following the initiation of AD. The overall aims of this systematic review were:

1) To identify all prospective studies that documented onset or change in RLS/WED symptoms after commencement of an AD.
2) Identify all prospective studies that measured change in PLMs following the commencement of an AD.
3) Compare risks of developing or worsening RLS/WED or PLMs across various AD.

Methods

This systematic review was conducted in accordance with the PRISMA guidelines [18].

Search strategy

We utilized the search terms “restless leg” or “willis ekbom” or “periodic leg movement” and “antidepressant” or “anti-depressant” or “antidepressive” along with the names of individual AD (complete list provided in Supplemental Materials) in Ovid MEDLINE, Embase and PsycINFO databases. The search was limited to English language publications. The databases were searched with no year restrictions until February 2016. Further details of the search strategy are provided in the Supplemental Materials.

Selection criteria

All abstracts identified by the initial search were reviewed by authors BPK and MPM. Any prospective study reporting onset or change in RLS/WED symptomatology and/or change in PLMs after initiation of an AD was eligible for inclusion. Our review was limited to human subjects and there were no age cut-offs. Case reports, correlational, cross-sectional, and retrospective studies potentially subject to recall and other biases were not included.

References of all articles that met criteria were reviewed for other studies that might satisfy inclusion criteria.

After initial review, full text articles of abstracts that met criteria were retrieved. Following review of the entire text, articles that continued to fit criteria were included in the review. The references of these articles were screened for additional studies that might qualify. In cases where only conference abstracts were available, we contacted the authors for full text articles or unpublished data. Any disagreements were resolved by discussion with the third author (JMB).

Once articles were identified and collated, the evidence provided by the study was graded utilizing the Oxford centre for evidence-based medicine guidelines in a blinded manner (Table 1).

Data extraction

Data from all studies that met inclusion criteria were systematically extracted by author BPK. The extraction was based on the PRISMA guidelines with reference to participants, intervention, comparisons, outcomes, and study design.

Results

Search results

The initial search of the databases revealed a total of 702 abstracts of interest. Following review of the abstracts, 27 articles appeared to meet criteria for inclusion. The remainder were unrelated to the primary objective of the review (605), case reports (36) or cross-sectional/retrospective studies (34) (Fig. 1).

Of the 27 abstracts identified, full text articles could be retrieved for a total of 25 articles. The remaining two were published as conference abstracts; full text manuscripts and/or unpublished data were unavailable despite attempts to contact the primary authors [19,20]. Following review of the full text articles, 17 articles met complete criteria. Thorough scrutiny of all the references from these articles identified one other study that met criteria for inclusion. Thus, a total of 18 studies were incorporated in the systematic review. There were no studies reporting the association between RLS/WED or PLMS and multiple other ADs included in the initial search. The medications that were included in the search are detailed in the supplement.

Of these 18 articles, three were small randomized placebo-controlled trials meeting evidence level of II. There were three single-blind placebo-controlled trials and the remainder was open-label trials and post-marketing surveillance studies (evidence level III). The studies that were selected are described in detail below and summarized in Table 2.

Table 1
Levels of evidence, modified from Oxford centre for evidence-based medicine guidelines levels of evidence working group.

Level of evidence	Study design
Level I	Systematic review of randomized controlled trials or large randomized controlled trials with narrow confidence intervals
Level II	Smaller randomized controlled trials
Level III	Non randomized controlled trials
Level IV	Case-series, case–control, or historically controlled studies
Level V	Mechanism-based reasoning