REVIEW ARTICLES

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Pharmacologically Induced/Exacerbated Restless Legs Syndrome, Periodic Limb Movements of Sleep, and REM Behavior Disorder/REM Sleep Without Atonia: Literature Review, Qualitative Scoring, and Comparative Analysis

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Background: Pharmacologically induced/exacerbated restless legs syndrome (RLS), periodic limb movements in sleep (PLMS), and REM behavior disorder/REM sleep without atonia (RSWA) are increasingly recognized in clinical sleep medicine. A scoring system to evaluate the literature was created and implemented. The aim was to identify the evidence with the least amount of confound, allowing for more reliable determinations of iatrogenic etiology.

Methods: Points were provided for the following criteria: manuscript type (abstract, peer-reviewed paper); population size studied (large retrospective study, small case series, case report); explicitly stated dosage timing; identification of peak symptoms related to time of medication administration (i.e., medication was ingested in the evening or at bedtime); initiation of a treatment plan; symptoms subsided or ceased with decreased dosage or drug discontinuation (for RLS articles only); negative personal history for RLS prior to use of the medication; exclusion of tobacco/alcohol/excessive caffeine use; exclusion of sleep disordered breathing by polysomnography (PSG); and PSG documentation of presence or absence of PLMS. For RLS and PLMS articles were also given points for the following criteria: each 2003 National Institutes of Health (NIH) RLS criteria met; exclusion of low serum ferritin; and exclusion of peripheral neuropathy by neurological examination.

Results: Thirty-two articles on drug-induced RLS, 6 articles on drug-induced PLMS, and 15 articles on drug-induced RBD/RSWA were analyzed.

Conclusion: Based on scores ≥ 10 and trials of medication reduction/cessation, the strongest evidence available for drug induced RLS are for the following drugs: escitalopram; fluoxetine; L-dopa/carbidopa and pergolide; L-thyroxine; mianserin; mirtazapine; olanzapine; and tramadol. Since none of the PLMS articles assessed PLMI in trials of medication reduction/cessation, the strongest evidence based on scores ≥ 10 are for the following drugs: bupropion, citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. Based on scores ≥ 10 and/or trials of medication cessation, the strongest evidence for drug induced RBD/RSWA is for the following drugs: clomipramine, selegiline, and phenelzine.

Keywords: Pharmacologically induced, periodic limb movements of sleep, rapid eye movement behavior disorder, REM sleep without atonia, restless legs syndrome

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Restless legs syndrome (RLS) is a sensorimotor disorder characterized by complaints of a strong urge to move the legs during periods of rest or inactivity (usually in the evening or night) that is relieved by movement.[1] RLS is rapidly becoming a widely recognized phenomenon with a range of pharmacological treatment options. With increased recognition of RLS more physicians are becoming aware that certain medications may induce RLS in their patients. Similar realizations are being made for patients with period limb movements in sleep (PLMS) and REM behavior disorder (RBD)/REM sleep without atonia (RSWA). There are many reports in the literature asserting pharmacologically induced RLS, PLMS, and RBD/RSWA; but the quality of the available evidence varies. These phenomena were likely not assessed in post-marketing surveillance studies of the medications mentioned in these reports. To establish true causation for drug-induced RLS the following features are useful: no prior history of the disease prior to drug initiation, ruling out other secondary causes (serum ferritin < 50 mcg/L,[2-4] renal failure,[5-7] peripheral neuropathy,[8-10] pregnancy,[7,11] excessive alcohol or caffeine use,[12,13] tobacco use[12]); dosage timing close to bedtime to help explain nocturnal symptoms; endorsement of all four 2003 National Institute of Health (NIH) criteria for definitive diagnosis of RLS[14]; and a polysomnogram (PSG) to rule out sleep disordered breathing as a cause of nocturnal disturbance that may be associated with RLS.[15] Secondary causes for PLMS and RBD/RSWA include excessive alcohol use for PLMS; and excessive alcohol and caffeine use for RBD/RSWA.[16-19] Most important for etiologic determination are trials on and off the offending medication with clinical re-assessment for changes in RLS, PLMS, or RBD/RSWA. In cases of PLMS and RBD/RSWA, multiple polysomnograms are necessary to assess changes in PLMS and RBD/RSWA on and off medication. We report a literature survey in which the evidence for

drug-induced RLS, PLMS, and RBD/RSWA are scored according to qualitative criteria. We also identify reports where trials of reduction in medication dosage or cessation of medication were performed. These results are used in combination with our scoring system to help identify the medications with the strongest evidence for inducing RLS, PLMS, or RBD/RSWA.

METHODS

We performed a PubMed search for all articles prior to January 2009 using the following terms alone and/or in combination: restless legs syndrome, RLS, periodic limb movements of sleep, PLMS, rapid eye movement behavior disorder, RBD, REM sleep without atonia, drug induced, and pharmacologically induced. We analyzed all papers that dealt with drug induced RLS, PLMS, and RBD/RSWA. The citation lists of these papers were also analyzed to find additional relevant articles.

A scoring system was created and implemented to evaluate the evidence. Two points were given to peer-reviewed papers; 1 point for published abstracts. Three points were given for large population studies, 2 for small series, and 1 for case reports. Additional points were then given for details that removed confounding factors in the determination of causation for drug induced movements. One point was given for each of the following criteria in the drug-induced RLS articles: explicitly stated dosage timing; medication ingested in the evening or at bedtime; initiation of a treatment plan for the RLS; RLS subsided or ceased with decreased dosage or drug discontinuation; negative personal history for RLS prior to use of the medication; exclusion of tobacco/alcohol/excessive caffeine use; each 2003 National Institutes of Health (NIH) RLS criteria endorsed[14]; exclusion of low serum ferritin; peripheral neuropathy excluded by neurological examination; sleep disordered breathing ruled out by PSG; and PSG documentation of presence or absence of PLMS. Maximum possible scores are listed in online **Table 7** (all tables for this article are available online only at www.aasmnet.org/jcsm). The 2003 NIH RLS criteria are: (1) an urge to move the limbs with or without sensation; (2) worsening at rest; (3) improvement with activity; and (4) worsening in the evening or night.

Similar scoring was applied to drug-induced PLMS and RBD/RSWA articles. Given the potential interrelation between RLS and PLMS, secondary causes of RLS were assessed in the PLMS literature. Individual articles analyzed in this review from here forward will be identified by the last name of the first author followed by the year of publication.

RESULTS

The PubMed search yielded 32 articles on drug-induced RLS—(31 peer-reviewed papers, 1 abstract), 6 articles on drug-induced PLMS (5 peer-reviewed papers and 1 abstract), and 15 articles on drug-induced RBD/RSWA (13 peer-reviewed papers and 2 abstracts). The headings for the data extraction table for RLS, PLMS, and RBD/RSWA articles are shown online **Tables 1-3**). **Table 4** online summarizes the extracted data. Thirty-one of 32 RLS articles were peer-reviewed papers. Dedrick et al. 2001 was the sole abstract evaluated for RLS; it did not mention specific medications. There were fewer articles on drug-induced PLMS or RBD/RSWA. There were few large retrospective studies in the RLS literature (4/31),[20-23] the PLMS literature (3/6),[24-26] and the RBD/RSWA literature (3/15).[27-29] The vast majority of the RLS literature is in the form of case reports (23/31).[30-51]

Few articles described whether patients were taking the offending medication resulting in RLS, PLMS or RBD/RSWA at or close to bedtime (RLS: 5/31,[40,41,43,51,52] PLMS: 1/6,[53] RBD/RSWA: 2/15[54,55]). Approximately one-third of the RLS articles (11/31)[22,32-34,36,37,39,41,42,44,47] clearly documented other medications the patient was taking; this was done in none of the PLMS articles and 5/15 of the RBD/RSWA articles.[27,56-59] Few articles ruled out secondary causes of RLS, PLMS, or RBD/RSWA. Excessive caffeine use was not ruled out in any of the articles assessed in this review. Tobacco use was ruled out in 2/31,[37,51] and excessive alcohol use was ruled out in 4/31[35,37,47,51] RLS articles. None of the PLMS or RBD/RSWA articles ruled out tobacco or alcohol use. Fourteen of 32 RLS articles ruled out renal failure,[22,33-35,38,41-44,48,50,60,61] 9/31 ruled out low serum ferritin or anemia,[34,37,38,42,43,47-50] and 3/31 ruled out peripheral neuropathy.[43,48,60] The article by Yang was the only PLMS article to rule out renal failure, low serum ferritin, and sleep disordered breathing; however, peripheral neuropathy was not ruled out.[26] Three of 31 RLS articles[38,49,50] and 1/15 RBD/RSWA[29] articles excluded sleep disordered breathing, a common mimic of RLS, PLMS, and RBD/RSWA. Ten RLS articles described women of childbearing age, and none of them explicitly used a negative β-human chorionic gonadotropin assay to rule out pregnancy.[20-22,30,31,34,42,44,51,62] Drake noted that a 30-year-old woman on methsuximide for epilepsy had regular menstrual cycles.[63]

Table 5 online shows the compiled scores for each article categorized by drug. **Table 6** online shows the articles in which RLS or RBD/RSWA subsided or ceased with reduction or withdrawal of medication. Based on scores ≥ 10 and the presence of trials of medication reduction/cessation, the strongest evidence available for drug induced/exacerbated RLS are for the following drugs: escitalopram,[51] fluoxetine,[34] L-dopa/carbidopa and pergolide,[43] L-thyroxine,[45] mianserin,[60] mirtazapine,[41,47] olanzapine,[38] and tramadol.[50] Vetrugno described a case of previously identified RLS exacerbated by tramadol use. Neither Bakshi (reporting a case of fluoxetine use) nor Santamaria (reporting a case of L-dopa/carbidopa and pergolide use) state if their patients had RLS prior to medication use. The remaining articles exclude RLS prior to medication use.

Since none of the PLMS articles assessed PLMI in trials of medication reduction/cessation, the strongest evidence based on scores ≥ 10 are for the following drugs evaluated by Yang in 2005: bupropion, citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[26] Based on an arbitrary score ≥ 10 (50% of the maximum possible score) and trials of medication reduction/cessation, the strongest evidence for drug induced RBD/RSWA is for the following drugs: clomipramine[27] and selegiline.[57] The article by Akindele is also considered strong evidence for drug induced RBD/RSWWA with a score of 8, because it was the only RBD/RSWA article with a repeat PSG off medication (phenelzine) to demonstrate discontinuation of RSWA.[56]

DISCUSSION

All the articles in this analysis were Level 4 evidence or higher according to the American Academy of Sleep Medicine Standards of Practice Committee rating of evidence for movements in sleep.[64,65] None of the articles analyzed in this study were Level 1, 2, or 3. All the studies analyzed in this review were either observational outcome studies or case series. Our scoring system was useful in assessing the current literature given the lack of controlled or uncontrolled randomized trials.

Medication timing was an issue in many of the articles analyzed. Potentially drug induced movements have to be correlated with dose timing and drug pharmacokinetics (i.e., time to peak plasma concentration and serum half-life). Drug induced movements would presumably occur most dramatically at the time of peak plasma concentration and during a window where there is remaining in the bloodstream depending on serum half-life. When medications that may induce nocturnal movement are not taken close to bedtime an accurate determination of causation is difficult, since peak plasma concentrations may be reached well before bedtime if the medications is taken at earlier times in the day. Also, if the medication serum half-life is short and the dosage timing is early in the day, serum levels of medication may be low or non-existent during time in bed in circadian related disorders such as RLS or sleep stage related disorders (PLMS, RBD/RSWA).

Determination of causation is complicated in patients with a clouded pharmacological milieu. Drug-drug interactions could lead to altered elimination times and for possible augmentation of drug-induced movements. Polypharmacy is more the rule than the exception for many patients. However, polypharmacy could be experimentally accounted for by repeated trials on-and-off the medication with the effects on nocturnal symptoms noted. Unfortunately this type of *repeated* trial was not performed in any of the RLS, PLMS, or RBD/RSWA articles analyzed. Assessing changes in PLMS or RBD/RSWA in repeated trials off medication is a financial challenge, since both are PSG-dependent diagnoses. One PLMS article (Ware) showed an increase in "nocturnal myoclonus index" above baseline with use of 200 mg per day of trimipramine or imipramine in patients who had movements in the baseline PSG on 75 mg per day of trimipramine or imipramine, respectively.[66] None of the remaining PLMS articles and none of the RBD/RSWA articles assessed PSG changes in movements in even a single trial on and off medications. The known nightly variation of PLMS makes this a challenge also.

Recent genetic studies have shown that the risk for RLS is strongly associated with PLMS.[67] Full understanding of the epidemiology and etiology of RLS necessitates PLMS assessment. Nine RLS articles assessed presence or absence of PLMS on PSG.[37,38,40,42,43,45,49,50,52] Five RLS articles assessed changes in concomitant PLMS with PSG on and off medication.[38,40,45,50,52] Kraus showed decreased PLMI (periodic limb movement index, per hour of sleep) from a PSG on olanzapine (PLMI: 39) to PSGs performed after one day off olanzapine (PLMI: 12) and one month off olanzapine (PLMI: 20).[38] Agargun performed 2 PSGs over consecutive nights before the initiation of mirtazapine that confirmed no PLMS prior to drug initiation.[40] A third PSG performed after one week of mirtazapine showed a PLMI of 41. Tan performed a PSG on L-thyroxine with a PLMI of 20, and a second PSG one month after L-thyroxine withdrawal with a PLMI of 10.[45] Prospero-Garcia showed an increased PLMI in 2 women from baseline PSGs performed after 2 weeks of fluoxetine use to repeat PSGs performed after 2 weeks on fluoxetine and mirtazapine.[52] The women (ages 63 and 50) had increases in PLMI of 30 to 32, and 41 to 56 respectively. A 41-year-old man from this study also had 2 similar PSGs performed and showed a decrease in PLMI on the combination of fluoxetine and mirtazapine from 67 to 61. Vertrugno showed a decrease in international RLS score from 30 to 9 and a slight decrease in PLMI from 142 to 138 after the discontinuation of tramadol and initiation of niaprazine, a sedating antihistamine.[50]

PLMS is highly variable from night to night. Except for Ware 1984, none of the articles on drug-induced PLMS assessed patients PLMI on medication across multiple nights. In an abstract publication, Ware showed that for patients with nocturnal myoclonus on 70 mg per day of trimipramine, nocturnal myoclonus increased with a titration of the dose to 200 mg per day.[66] Exact quantification of PLMIs was not provided in the abstract. In the articles on drug-induced RLS that evaluated PLMS, none of the articles assessed PLMI on multiple nights of drug use. Conflicting results like those presented by Prospero-Garcia, and small increases in PLMI in one PSG on medication like those presented by Kraus, Tan, and Vertrugno are difficult to interpret without the use of multiple PSGs or multi-night actigraphy during medication use.[38,45,50,52]

Endorsement of the 2003 NIH RLS criteria is another area of variability from report to report. Only 11 drug induced RLS articles met all 4 RLS criteria by presenting all 4 criteria in the case history or explicitly stating that all 4 RLS criteria were met.[22,33,34,42,44,45,48-51,60] Four of 32 RLS articles endorsed none of the RLS criteria.[21,23,36,68] Of the articles about drug-induced PLMS, only Salin-Pascual made reference to the development of RLS symptoms in 2 patients of a cohort of 8.[53] None of the PLMS articles evaluated patients according to NIH consensus criteria. This is problematic not only for the RLS articles, since drug-induced RLS can probably only be assessed in patients who endorse all 4 criteria, but also for the PLMS articles, given the close interrelation of these phenomenon revealed by recent genetic data.[67] Stefansson et al. has shown that self-administered 4/4 consensus criteria endorsement agrees with expert clinical diagnosis approximately 74% of the time.[67] Even when patients endorse all 4 consensus criteria, they may still have conditions that mimic RLS, such as sleep disordered breathing and diabetic neuropathy. Assessment of family history of RLS may be useful in that a negative family history may help rule out idiopathic RLS. Actigraphy would also be helpful in evaluating for RLS or PLMS across multiple nights. Actigraphy was not used in any of the articles analyzed.

Ruling out alcohol, tobacco, or excessive caffeine use are done by taking a relevant clinical history. Ruling out pregnancy in women of child bearing age; elevated blood urea nitrogen; elevated serum creatinine; or a low serum ferritin require appropriate laboratory testing. Serum testing for

hyperthyroidism may also be useful given Tan's report of L-thyroxine induced RLS.[45] Other factors that may also be useful to assess in patients with RLS, PLMS, or RBD/RSWA include behaviorally induced insufficient sleep syndrome and lack of exercise. The Michigan Neuropathy Screening Instrument is a validated questionnaire that sleep physicians can use that allows for quick screening for peripheral neuropathy with 15 simple "Yes" or "No" questions.[69,70]

Assessment of patients with drug induced RLS, PLMS, or RBD/RSWA may provide insights into the underlying pathophysiology of these disorders. For example, Santamaria described a patient in whom the discontinuation of a trial of L-dopa and the discontinuation of a trial of pergolide both led to the cessation of RLS symptoms.[43] Though multiple trials on and off L-dopa/carbidopa or pergolide were not performed, RLS symptoms with dopamine or dopamine agonists are similar to the augmentation of RLS with dopamine and dopamine agonists and may share a common mechanism.[43]

RBD/RSWA overlaps were not addressed using the 2007 AASM Scoring Manual criteria of subdividing REM epochs into 10 three-second mini-epochs was not clearly used by any of the RBD/RSWA articles reviewed.[71] Without a standard method to assess RBD/RSWA, conclusions are difficult to draw from the available literature. Also, RBD/RSWA may be secondary to a range of comorbid neurological conditions including Parkinson disease and narcolepsy. Two of 15[57,59] and 4/15[27,55,72,73] RBD/RSWA articles analyzed patients with comorbid Parkinson disease and narcolepsy, respectively. Assessment of drug-inducement of RBD/RSWA in patients with these comorbidities requires repeated trials on-and-off medication with standardized assessment of the REM epochs using AASM scoring criteria for RBD/RSWA. This was done in none of the articles analyzed. Five of 15 RBD/RSWA had patients who did not exhibit clinical manifestations of RBD.[27,29,54,74,75] Patients with RSWA may progress into clinically significant RBD, but the rate is unknown. As a result, the risk of developing clinically significant RBD from drug-induced RSWA is also unknown.

Future studies of RLS, PLMS and RBD/RSWA must take into account drug use given the widespread use of many of the medications described in this review, especially SSRI antidepressant medications. For the treating clinician, awareness of the medications that can potentially lead to RLS, PLMS, or RBD/RSWA is crucial because it changes treatment strategy. Instead of starting another medication such as a dopamine agonist to treat iatrogenic RLS or PLMS, or clonazepam to treat iatrogenic RBD/RSWA, it may be more prudent to withdraw the potentially offending medication as a first line intervention. For the researcher, awareness of these observations may facilitate development of more effective future studies and foster translational applications to the care of our patients. reuptake inhibitors. Subclinical RBD in Schenck 1992 is defined as increased electromyogram tone in REM with no specific clinical correlates. PLMI: periodic limb movement index. AHI: apnea hypopnea index. QID: four times a day. PLMS: Periodic limb movements of sleep. OSA: obstructive sleep apnea. TCA: tricyclic antidepressants. RSWA: REM sleep without atonia. Tmax: time to maximum serum concentration. T1/2: serum half-life.

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Table 1—Literature on pharmacologically induced/exacerbated restless legs syndrome (RLS) ordered by publication date.

Area shaded gray is the key for Table 1

Reference—Drug, Dosage Used					
• **Drug mechanism of action**	• **Other medications**	**Number of patients evaluated, age, sex (for women of child bearing age, is a negative β-hCG documented)**	**2003 NIH RLS diagnostic criteria met*****	**Normal serum BUN and creatinine**	**PSG documenting PLMS**
		Tobacco use evaluated	**Did patient have RLS features prior to using the drug?**		
• **T1/2, Tmax**	• **Treatment for RLS → Response to treatment**	**Caffeine use evaluated**	**2003 NIH RLS criteria not clearly met**	**Normal serum Ferritin**	**PSG excluding OSA**
• **Timing of medication dosage**		**Alcohol use evaluated**		**Peripheral neuropathy explicitly excluded**	
Heiman et al. 1986[30]—Lithium, 1800 mg/day					
• Increased intraneuronal catecholamine metabolism • Altered sodium channel permeability	• Unknown	1, 48, female (No)	(1), (4)	Unknown	No
		No	Yes		
• 20-24 h, 2-4 h	• Lithium was withdrawn → RLS subsided • Lithium restarted with clonazepam 2 mg at bedtime → failed	No	(2), (3)	Unknown	No
• Unknown		No		No	
Myers et al. 1986[31]—Clomipramine, 200 mg/day					
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• Unknown	1, 49, female (No)	(3)	Unknown	No. A "sleep EEG" revealed myoclonus.
		No	No		
• 19-37 h; 2-6 h	• Clonazepam 0.5 mg/night → RLS ceased	No	(1),(2),(4). Patient experienced nocturnal myoclonus, and nightmares on clomipramine.	Unknown	No.
• Unknown		No		No	
Drake et al. 1988[63]—Patient 1: Methsuximide, dose unknown; Patient 2: Phenytoin, dose unknown, phenytoin level: 19 mg/L					
• Methsuximide: anticonvulsant succinimide • Phenytoin: anticonvulsant that mediates voltage dependent sodium and calcium channels	• Patient 1: Phenytoin, carbamazepine • Patient 2: Unknown	2, Patient 1: 30, female (No, patient having menstrual cycles); Patient 2: 56, male	Patient 1: (1) Patient 2: (1), (4)	Patient 1: Yes Patient 2: Yes	No
		No	No		
• Methsuximide: 2-3 h, unknown • Phenytoin: 7-42 hours, 4-12 h	• Patient 1: Switched from methsuximide to valproate → RLS ceased • Patient 2: Switched from phenytoin to carbamazepine → RLS subsided	No	Patient 1: (2), (3), (4) Patient 2: (2), (3)	Patient 1: Ferritin unknown, no anemia Patient 2: Ferritin unknown, no anemia	No
• Unknown		No		Patient 1: Yes Patient 2: Yes	

Table 1 continued on following page

Table 1 *(continued)*

Paik et al. 1989[60]—Mianserin, Patient 1: 90 mg/day; Patient 2: 60 mg/day; Patient 3: 90 mg/day					
• Adrenergic alpha antagonist • Histamine H1 antagonist • Serotonin antagonist	• Unknown	3; 44, 45, 49; all male	1: (1), (2), (3), (4) 2: (1), (4) 3: (3), (4)	1: Unknown 2: Normal comprehensive labs 3: Unknown	No
		No	No		
• 1 h, 3 h	Patients 1-3 • 1: Added diazepam 10 mg/day and hot pad → failed; Switch from mianserin to amitriptyline 100mg/day → RLS ceased • 2: Switch from mianserin to amitriptyline 10 mg/day → RLS ceased • 3: ↓dose of mianserin dose from 90 to 30 mg/day → RLS subsided	No	1: None 2: (2), (3) 3: (1), (2)	1: Ferritin unknown, normal iron 2: Ferritin unknown, no anemia 3: Ferritin unknown, no anemia	No
• Unknown		No		All three had normal neurological examinations	
Terao et al. 1991[32]—Lithium, 800 mg/day					
• Increased intraneuronal catecholamine metabolism • Altered sodium channel permeability	• Levomepromazine 5-25 mg/day. Discontinued to help rule it out as a cause of RLS. RLS persisted after discontinuation.	1, 18, male	(1)	Unknown	No
		No	Unknown		
• 20-24 h, 2-4 h	• L-tryptophan dose unknown taken intermittently → partial relief of crawling sensation. • Decrease of lithium to 400 mg/day → RLS ceased	No	(2), (3), (4)	Unknown (Normal serum iron)	No
• Unknown		No		No	
O'Sullivan et al. 1993[33]—Cimetidine, 1200 mg/day					
• Histamine H2 receptor antagonist	• Prednisone taper	1, 65, female	(1), (2), (3), (4)	Normal	No
		No	Unknown		
• 2 h, 45–90 min	• Clonazepam 6 mg/day → RLS subsided • Propranolol 20 mg/day → RLS subsided • Acetaminophen with codeine 600 mg/60 mg per day → RLS ceased	No	None	Unknown (marginally low serum iron: 188 pg/mL)	No
• Unknown		No		No. Patient had poliomyelitis.	
Bakshi et al. 1996[34]—Fluoxetine, 60 mg/day					
• SSRI	• Oral contraceptives	1, 22, female (No)	(1), (2), (3), (4)	Normal	No
		No	Unknown		
• 1-3 days, 6-8 h	• Fluoxetine discontinued → RLS ceased 6 weeks later	No	None	Normal	No
• Unknown		No. No history of "substance abuse."		No	
Sanz-Fuentenebro et al. 1996[35]—Paroxetine, 20 mg/day					
• SSRI	• Unknown	1, 33, male	(1), (3), (4)	Normal routine blood and urine tests	No
		No	No		
• 21 h; 5 h	• Lormetazepam 1mg before bed → RLS subsided	No	(2)	Not available	No
• morning		Infrequently consumes small amounts of alcohol		No	

Table 1 continued on following page

Table 1 *(continued)*

Markkula et al. 1997[62]—Mianserin, 30-90 mg/day					
• Adrenergic α antagonist • Histamine H1 antagonist • Serotonin antagonist	Patients 1-6: 1. Unknown 2. Unknown 3. Alprazolam 3 mg/day 4. Unknown 5. Unknown 6. Doxepin 100 mg/day	6; 54, 71, 29, 59, 78, 53; 2 men and 4 women (No) • Patients 1, 3, 5: had motor restlessness before mianserin was started. Only patient 5 had mianserin explicitly exacerbate previous symptoms • Patient 2, 4, 6: RLS was proceeded by mianserin use	(1)	No *	No
		No	1: Familial RLS 2: Unknown 3: Motor restlessness 4: Unknown 5: Familial RLS 6: Unknown		
• 1 h, 3 h	Patient 1 • Clonazepam → failed • Carbamazepine → failed • Levodopa-benserazide → RLS subsided and returned • Temazepam → failed • Opioid analgesics → failed • Switch from mianserin to trazodone → RLS ceased Patient 2 • Switch from mianserin to doxepin and flupenthixol → RLS ceased Patient 3 • Switch from mianserin to fluvoxamine → RLS ceased Patient 4 • Switch from mianserin to clonazepam → RLS ceased Patient 5 • Levodopa-carbidopa → RLS subsided but returned with time; • The following used without mianserin: diazepam, oxazepam, clonazepam, chlordiazepoxide, amitriptyline, citalopram → all failed Patient 6 • Doxepin discontinued → failed • mianserin dose reduced from 60 mg/day to 30 mg/day → RSL ceased	No	(2), (3), (4)	No * (*: patients were evaluated to exclude "general medical conditions behind" the RLS)	No
• Unknown		No		No	
Hargrave et al. 1998[36]—Sertraline, 25 mg/day					
• SSRI	• Lorazepam 1 mg/day	1, 75, male	Unknown	No	No
		No	Yes		
• 62-100 h; 4-8 h • morning	• None	No No	Unknown	No No	No

Table 1 continued on following page

Table 1 *(continued)*

Horiguchi et al. 1999[37]—Haloperidol 3mg/day					
• Neuroleptic • Dopamine antagonist • Minor antihistaminergic and anticholinergic properties	• Biperiden 3 mg/day	1, 51, male	(1)	Unknown	Yes. Total # of PLMs: 65 Mean intermovement interval: 33 sec Unknown whether criteria met for PLMS
		Yes. No tobacco use.	Unknown		
• 3 weeks; 6 days	• Switched from biperiden to trihexyphenidyl 6 mg/day and flunitrazepam 2 mg/day. (Haldol continued unchanged) → failed	No	(2), (3), (4)	Normal	Not explicity stated
• Unknown		Yes. Denied alcohol abuse.		No	
Kraus et al. 1999[38]—Olanzapine, 20 mg/day					
• Atypical antipsychotic	• Unknown	1, 41, male	(2), (3), (4)	Normal routine labs	Yes 1st PSG on olanzapine 20 mg/day: PLMI=39 2nd PSG off olanzapine for one day: PLMI=12 3rd PSG off olanzapine for 1 month: PLMI=20
		No	No		
• 21 to 54 h, 6 h	• Decrease of olanzapine from 20 mg/day to 10 mg/day → RLS subsided • Discontinuation of olanzapine → RLS ceased	No	(1)	Normal. Normal iron as well.	Yes. No evidence OSA on all three studies.
• Unknown		No		No	
Bonin et al. 2000[39]—Mirtazapine, 15 mg/day					
• post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Zopiclone 7.5 mg/day; Valpromide 300 mg/day	1, 33, male	(2), (4)	Unknown	No
		No	Unknown		
• 20-40 h; 2 h	• Switch from mirtazapine to fluvoxamine 100 mg/day → RLS ceased	No	(1), (3)	Unknown	No
• Unknown		No		No	
Dimmitt et al. 2000[20]—Sertraline, 29 patients; Paroxetine, 34 patients; Fluoxetine, 3 patients, Doses varied					
• SSRI	• Unknown	66; age range: 19 to 86, mean age unknown; 65% female	(1), (4)	Unknown	No
		No	(2), (3)		
• Various medications	• Patients with RLS prior to use of SSRI: 43 (65%) SSRI → RLS subsided (25 patients) SSRI → RLS ceased (5 patients) SSRI → no change in RLS (13 patients) • Patient without RLS prior to use of SSRI: 23 patients (34%) SSRI → developed RLS (2 patients)	No		Unknown	No
• Unknown		No		1 patient with diabetic peripheral neuropathy. Pre-existing RLS subsided with SSRI use.	

Table 1 continued on following page

Table 1 *(continued)*

Dedrick et al. 2001*[21]—Specific medications not specified					
• TCA: 13 patients • SSRI: 17 patients • "Other': 18 patients	• Unknown. Patients in the "other" category may have used more than one type of antidepressant. • 49 patients with RLS. 26 on antidepressants, 23 were not.	100 consecutive patient chart review; mean age: 53.9 ±14.8; 62 male, 38 female	Unknown Unknown	Unknown	No
• Unknown • Unknown	• No	Unknown Unknown	Unknown	Unknown No	No
Agargun et al. 2002[40]—Mirtazapine, 30 mg/day					
• post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Unknown	1, 45, male No	(2), (4) Unknown	Unknown	Yes. 1st and 2nd PSG performed over two consecutive nights before mirtazapine treatment: no PLMS documented 3rd PSG performed after a week of mirtazapine: PLMI=41
• 20-40 h; 2 h • evening	• Clonazepam 1 mg/day added → RLS subsided	No No	(1), (3)	Unknown No	
Bahk et al. 2002[41]—Mirtazapine, 15 mg/day					
• post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Alprazolam 0.5 mg/day	1, 56, female No	(3) No	Normal blood chemistry	No
• 20-40 h; 2 h • Evening	• Clonazepam 0.5 mg/day added for 7 days → failed • Switching mirtazapine to paroxetine → RLS ceased	No No	(1), (2), (4)	Unknown No	No
Wetter et al. 2002[42]—Risperidone, 6 mg/day					
• Atypical antipsychotic • D2 receptor antagonist • 5-HT2 receptor antagonist	• Valproic acid 900 mg/day	1, 31, female (No) No	(1), (2), (3), (4) Unknown	Normal routine labs	Yes. 1st PSG done on risperidone 4 mg/day: PLMI=12.6 2nd PSG done on quetiapine 400 mg/day: PLMI=1.5
• 3-20 h, 1 h • Unknown	• Dose of risperidone decreased to 4 mg/day → failed • Switch from risperidone to haloperidol 10 mg/day → failed • Switch from haloperidol to quetiapine 400 mg/day → RLS ceased	No No	None	Normal ferritin and iron No	Not explicitly stated

Table 1 continued on following page

Table 1 *(continued)*

Leutgeb et al. 2002[22]—TCAs: Amitriptyline, Trimipramine, Clomipramine, Doxepin, Dibenzepin, Imipramine, Maprotiline, Opipramol, Nortriptyline. SSRIs: Paroxetine, Fluoxetine, Sertraline, Citalopram. Number of patients on each medication unknown. Dosages varied.					
• TCA • SSRI	• Neuroleptics: Fluspirilene, Sulpiride, Flupentixol, Zotepine, Perphenazine, Levomepromazine, Thioridazine, Promethazine, Perazine, Melperone, Bromperidol, Triflupromazine, Prothipendyl, Haloperidol, Risperidone • Metoclopramide • Non-opioid analgesics	243 patients interviewed before and >6 months after initiating antidepressant treatment; Mean age: 44.7 ± 11.3; 64 % female	(1), (2), (3), (4)	No patients with a history of renal failure.	No
		No	Unknown		
• Various medications	• No	Yes. 11 RLS patients drank 5+ cups of coffee per day (all of these patients were also on non-opioid analgesics). 6 non-RLS patients drank 5+ cups of coffee per day.	None	Unknown. No patients with a history of anemia.	No
• Unknown		No		No	
Santamaria et al. 2003 **[43]—Two medications used to treat PLMS. Sinemet CR: Levodopa, 300 mg at bedtime (carbidopa dose unknown) and levodopa, 100 mg at 4am (carbidopa dose unknown). Pergolide, 0.60 mg/day at bedtime,					
• L-dopa: Dopamine • Pergolide: ergot derived dopamine receptor agonist	• Unknown	1, 50, male	(1), (4)	Normal "blood tests"	Yes 1st PSG before L-dopa therapy: PLMI=102 2nd PSG after 7 months of L-dopa therapy: PLMI=13
		No	Unknown		
• L-dopa: 1.5 h, 2 h • Pergolide: 27 h, 2-3 h	• Discontinuation of L-dopa → RLS ceased, effect on PLMS not stated • Pergolide started → RLS returned, PLMS movements decreased • Discontinuation of pergolide → RLS ceased and PLMS returned	No	(2), (3)	Low normal ferritin: 31 mcg/L, 60 mcg/L	Not explicitly stated
• L-dopa: Bedtime and 4am • Pergolide: Bedtime		No		Normal neurological examination. Normal EMG examination (muscles tested not described).	
Chen et al. 2003[44]—Zonisamide, 200 mg twice a day					
• Voltage gate calcium channels and sodium channel blockade	• None	1, 27, female (No)	(1), (2), (3), (4)	Normal	No
		No	No		
• 60 h, 2-6 h	• Decrease dosage of zonisamide from 400 mg every day to 400 mg/day alternating with 300 mg/day → RLS subsided • Ferrous sulfate 325 three times a day for 2 months → failed	No	None	Low ferritin: 42 ng/mL	No
• Twice a day		No		No	

Table 1 continued on following page

Table 1 *(continued)*

Tan et al. 2004[45]—L-thyroxine, 1000 µg/day					
• Thyroid hormone	• Unknown	1, middle aged, male	(1), (2), (3), (4)	Unknown	Yes. 1st PSG done during L-thyroxine therapy: PLMI=20 2nd PSG done one month after L-thyroxine withdrawal: PLMI=10
		No	No		
• 7 days,	• Discontinuation of L-thyroxine → RLS subsided (↓ RLS score from 24 to 6), and PLMS subsided (↓ PLMI from 20 to 10)	No	None	Low ferritin: 10 ng/mL	Not explicitly stated
• Unknown		No		No	
Pae et al. 2004[61]—Patient 1: Mirtazapine, dose unknown; Patient 2: Mirtazapine, 30 mg					
• post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Patient 1: unknown • Patient 2: unknown	2. Both female. Patient 1: 56; Patient 2: 58	Patient 1: none Patient 2: (2)	Patient 1: no laboratory abnormalities Patient 2: no laboratory abnormalities	No
		No	No		
• 2 h, 20-40 h	• Patient 1: None • Patient 2: None	No	Patient 1: (1) – (4) Patient 2: (1), (3), (4)	Unknown	No
• Unknown		No		No	
Brown et al. 2005[23] TCAs: 21 patients - Amitriptyline (16), Imipramine (2), Nortriptyline (3), Clomipramine (1). SSRIs: 36 patients - Fluoxetine (17), Paroxetine (8), Sertraline (9) Other: Bupropion (7), Buspirone (3), Lithium (1), Mirtazapine (2), Venlafaxine (4), Nefazodone (5), Trazodone (18).					
• Various medications	• Unknown	200 consecutive charts reviewed	Unknown. 45% of patients met "clinical criteria" for RLS.	Unknown	No
		No			
• Various medications	• No significant correlation found between antidepressant use and RLS	No	Unknown	Unknown	No
• Unknown		No		No	
Earley et al. 2006 **[68]—Tramadol, 100-300 mg/day					
• Synthetic opioid analgesic	• Unknown	9 patients on tramadol from a clinical database of unknown number of patients	Unknown. 4 patients experienced augmentation of previous RLS. 7 of 9 patients were given tramadol to treat RLS.	Unknown	No
		No			
• 2 h, 6 h	• 2 patients discontinued tramadol → return to pre-treatment RLS severity	No	Unknown	Unknown	No
• Unknown		No		2 patients had evidence of small fiber neuropathy	
Ozturk et al. 2006[46]—Paroxetine, 60 mg/day					
• SSRI	• None	1, 36, male	(3), (4)	Unknown	No
		No	No		
• 21 h; 5 h	• Decreased dose of paroxetine to 50 mg/day → RLS subsided (↓RSL score from 32 to 19) • Paroxetine 60 mg/day and oxcarbazepine 300 mg/day → RLS subsided (RLS score of 8)	No	(1), (2)	Unknown	No
• Unknown		No		No	

Table 1 continued on following page

Table 1 *(continued)*

Chang et al. 2006[47]—Mirtazapine, 60 mg/day					
• post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Domperidone, dose unknown	1, 32, Male	(1),(2),(4)	Unknown	No
		No "substance abuse."	No		
• 20-40 hours; 2 hours	• Clonazepam 2mg/day → Failed • Switching of mirtazapine to cirzodone → RLS ceased	No	(3)	Normal ferritin level	No
• Unknown		Yes. No alcohol abuse.		Normal EMG and NCV studies. Muscles tested unknown.	
Prospero-Garcia et al. 2006[52]—Fluoxetine, 20 mg/day; Mirtazapine, 15 mg/day					
• Fluoxetine: SSRI • Mirtazapine: post-synaptic 5-HT_2 and 5-HT_3 antagonist • Post-synaptic 5-HT_1 agonist • Pre-synaptic α2 agonist	• Unknown	3 Age: Females: 63, 50; Male: 41 Sex: 2 females; 1 male	(3),(4)	Unknown	1st PSG: after 2 weeks of fluoxetine use. 2nd PSG: after 2 weeks of fluoxetine and mirtazapine. Women Δ in PLMD index: 30 →32; 41 → 56 Man Δ in PLMD index: 67 → 61
		No	No		
• T1/2: Fluoxetine: 1-3 days. Mirtazapine: 20-40 h • Tmax: Fluoxetine: 6-8 h. Mirtazapine: 2 h	• No	No	(1), (2)	Unknown	No
• Nightly		No		No	
Perroud et al. 2007[48]—Paroxetine, 20 mg/day					
• SSRI	• Unknown	1, 48, female	(1), (2), (3), (4)	Normal routine blood screening	No
		No	No		
• 21 h, 5 h	• Switch from paroxetine to citalopram 60 mg/day → RLS worsened	No	None	Normal ferritin level	No
• Unknown		No		Normal neurological examination	
Abril et al. 2007[49]—Sodium oxybate (γ-hydroxybutyrate), 9 g/day					
• Binds to GABA-B and GHB receptors	• Unknown	1, 52, male	(1), (2), (3), (4)	Unknown	Yes PSG performed prior to use of GHB: PLMI=17
		No	No		
• 0.5-1.25 h, 0.5-1 h	• Discontinuation of sodium oxybate → RLS ceased (↓RLS score from 30 to 0)	No	None	Normal ferritin and iron.	Yes. Apnea-hypopnea index=5. Patient has mild OSA.
• Unknown		No		No	
Vetrugno et al. 2007 **[50]—Tramadol, 100 every 2-3 h					
• Synthetic opioid analgesic	• Unknown	1, 86, female	(1), (2), (3), (4)	Normal	Yes. 1st PSG done on tramadol: PLMI=142 2nd PSG done 2 months after switch from tramadol to niaprazine: PLMI=138
		No	Yes		
• 2 h, 6 h	• Switched from tramadol to niaprazine 30 mg/every night → RLS subsided (↓ RLS score from 30 to 9), PLMS subsided (↓ PLMI from 142 to 138)	No	None	Normal	Yes. No chest and abdominal leads were used in the PSG. OSA was ruled out by finger pulse oximetry and larynx microphone
• 10am, 1pm, 4pm, 6pm, 8pm, 1pm		No		No	

Table 1 continued on following page

Table 1 *(continued)*

Page et al. 2008[51]—Escitalopram, 20 mg/day					
• SSRI	• Unknown	1, 34, female (No)	(1), (2), (3), (4)	Increased BUN: 36 mg/dL (normal: 6-23 mg/dL) Increased creatinine: 1.6 mg/dl. Baseline 1.3 mg/dL; normal range: 0.4-1.2 mg/dL)	No
		Denied tobacco use	No		
• 27-32 h, 5 h	• Cyclobenzaprine 5 mg every 4 h as needed → failed • Discontinuation of escitalopram and switching of cyclobenzaprine to lorazepam 0.5 mg every 4 h → RLS subsided (↓ RLS score from 32 to 2)	No	None	Normal ferritin: 100 ng/mL	No
• Bedtime		Denied alcohol use		No	

Brown 2005 showed no significant correlation between antidepressant use and RLS symptoms. Dimmit 2000 showed that SSRI may actually improve RLS symptoms in some patients. All other reports show worsening of RLS with medications used.
*Reference is a published abstract (Dedrick 2001).
**Sinemet, pergolide, tramadol are commonly used to treat RLS. Sinemet and pergolide induced RLS. Tramadol augmented previously present RLS.
***2003 NIH diagnostic criteria include the following: (1) an urge to move the limbs with or without sensations, (2) worsening at rest, (3) improvement with activity, and (4) worsening in the evening or night.[14] Frequency of RLS symptoms with medication use was difficult to assess from the reports listed.
β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; EEG, electroencephalogram; GABA, gamma-amino-butyric-acid; GHB, gamma-hydroxy-butyrate; PLMI, periodic limb movement index; EMG, electromyogram; OSA, Obstructive sleep apnea; NIA, neuroleptic induced akathisia; NCS, nerve conduction study; PLMS, periodic leg movements of sleep; PLMI, periodic limb movement index; PSG, polysomnogram; SSRI, selective serotonin reuptake inhibitor; Tmax, time to maximum serum concentration; T1/2, serum half-life; NIH, National institutes of health; TCA, tricyclic antidepressants; Δ, change.

Table 2—Literature on pharmacologically induced periodic limb movements of sleep (PLMS) ordered by publication date.

Area shaded gray is the key for Table 2

Reference				
Drugs evaluated, Time of medication dosage	**Number of patients, mean age ± standard deviation**	**Number of patients who developed RLS with medication**	**Normal serum BUN and creatinine**	**PSG documenting PLMS**
	Tobacco use evaluated		**Normal serum Ferritin**	
Other medications	**Caffeine use evaluated**	**2003 NIH RLS criteria met**	**Peripheral neuropathy excluded**	**PSG excluding OSA**
	Alcohol use evaluated	**Treatment of RLS → Response to treatment**		
Ware et al. 1984*[66]				
Trimipramine Imipramine Dosage for each was titrated from 75 mg/day to 200 mg/day over 20 days Timing of medications unknown	Trimipramine: 13 patients, age unknown Imipramine: 14 patients, age unknown	Not evaluated	Unknown	Yes. PSGs were performed before titration and during the titration. Antidepressant use increased nocturnal myoclonus index in patients who had movements in the baseline PSG. Specific PLMIs not provided.
	No		Unknown	
Unknown	No	Not evaluated	No	Not explicitly stated.
	No	Not evaluated		
Garvey et al. 1987[24]				
Imipramine 45 patients Desipramine 25 patients Amitriptyline 16 patients Doxepin 5 patients Trazodone 4 patients Nortriptyline 2 patients Maprotiline 2 patients Doses unknown, timing of medication unknown	98, 40 ± 14	Not explicitly stated. 2 patients developed "nocturnal myoclonus" involving upper and lower extremities, starting shortly after sleep onset, and lasting most of the night. The drugs used in these cases are unknown.	Unknown	No
	No		Unknown	
Unknown	No	Unknown	No	No
Dorsey et al. 1996[76]				
Fluoxetine 10 mg/day (1 patient) 20 mg/day (2 patients) 40 mg/day (3 patients) 80 mg/day (2 patients) Timing of medications unknown	9; 25 ± 6; 77% female	Not evaluated	Unknown	Yes. PLM arousal was elevated in 4 patients Patient on fluoxetine 10 mg/day: 8 Patient on fluoxetine 20mg/day: 15 Patient on fluoxetine 40 mg/day: 8 Patient on fluoxetine 80 mg/day: 9
	No		Unknown	
Unknown	No	Not evaluated	No	Not explicitly stated.
	No	Not evaluated		
	No	None		
Hussain et al. 1997*[25]				
Fluoxetine Sertraline Amitriptyline Paroxetine Dosages unknown, timing of medications unknown	Fluoxetine: 56 patients, 39.7 ± 11.6 Sertraline: 21 patients, 41.6 ± 16.8 Amitriptyline: 16 patients, 50.4 ± 10.3 Paroxetine: 12 patients, 43.2 ± 16.8	Not evaluated	Unknown	Yes. PLMI for all patients: median = 4, (range: 0-52). 43% had PLMI > 5. No significant differences between the different medications.
	No		Unknown	
Unknown	No	Not evaluated	No	Not explicitly stated.
	No	Not evaluated		

Table 2 continued on following page

Table 2 *(continued)*

Salin-Pascual et al. 1997[53]				
Venlafaxine First 2 nights: 75 mg/day Next 2 nights: 150 mg/day Medication were taken at 2100 h, 1 h after start of PSG	8; 29 ± 9; 37% female	2/8 patients developed RLS.	Unknown	Yes. 6/8 patients had PLMS observed on PSG. PLMI was 25 for these 6 patients.
	No		Unknown	
None	No	Unknown	No	Not explicitly stated
	No	None		
Yang et al. 2005[26]				
Bupropion 238 mg ±87 mg Venlafaxine 157 ± 101 mg SSRI: Citalopram 30 ± 13 mg, fluoxetine, 37 ± 20, paroxetine 27 ± 12, sertraline 124 ± 63 Timing of medication unknown	Bupropion: 34 patients, 34 y ± 1 Venlafaxine: 49 patients, 39 y ± 1 SSRI: 191 patients,38 ± 0.6	Not evaluated	Yes	Yes. PLMIs: Bupropion 43 ± 1.1 Venlafaxine 13.6 ± 2.1 Citalopram 14.0 ± 2.0 Fluoxetine 13.6 ± 2.3 Paroxetine 9.6 ± 2.5 Sertraline 12.7 ± 2.1
	No		Yes	
No other antidepressant medication. Other medications unknown.	Yes	Not evaluated	No	Yes
	Yes	Not evaluated		

*Reference is a published abstract (Hussain 1997).

Table 3—Literature on drug-induced REM behavior disorder (RBD) ordered by publication date.

Area shaded gray is the key for Table 3

Reference—Drug, Dosage Used				
• **Drug mechanism of action**	• **Other medications**	**Number of patients evaluated, Age, Sex** **Tobacco use evaluated**	**PSG documenting PLMS**	**Co-morbid condition**
• **T1/2, Tmax** • **Timing of medication dosage**	• **Treatment for RBD → Response to treatment**	**Caffeine use evaluated** **Alcohol use evaluated**	**PSG documenting OSA**	**Clinical Manifestations of RBD present**
Akindele et al. 1970[56]—Phenelzine, 45-60 mg/day				
• Monoamine oxidase inhibitor	• Patients A and B: nialamide • Rest of the patients: unknown	7; Patients A, B, F, G are "young adults" and are all male. Patients M, R, K have a mean age of 47 and are all female. No	PLMS not mentioned	A, B, F, G: normal M, R, K: psychiatric
• 11 h, 43 min • Unknown	• Discontinuation of phenelzine → RSWA ceased	No Yes. Patients had no alcohol use.	Sleep disordered breathing not mentioned	G, F, M: had vivid dreams All 7 patients had RSWA.
Guilleminault et al. 1976[27]—Clomipramine, 100 mg/day				
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• 17/21 patients were on methylphenidate and/or amphetamine	21, mean age 37, 10 male No	PLMS not mentioned	Narcolepsy
• 19-37 h, 2-6 h • 25 mg QID, 8 AM, 12 PM, 3 PM, 5 PM	• Discontinuation of clomipramine → effect on RSWSA unknown	No No	Sleep disordered breathing not mentioned	No
Besset 1978[74]—Clomipramine, 100-175 mg/day				
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• Unknown	7, mean age unknown, age range 20-25, 5 male No	PLMS not mentioned	Normal
• 19-37 hours, 2-6 hours • Unknown	• Discontinuation of clomipramine → effect on RSWA unknown	No No	Sleep disordered breathing not mentioned	No
Bental et al. 1979[72]—Clomipramine, 75 mg/day				
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• Unknown	1, 52, female No	PLMS not mentioned	Narcolepsy
• 19-37 hours, 2-6 hours • Unknown	• Decrease dosage of clomipramine → failed	No No	Sleep disordered breathing not mentioned	Yes
Schenck 1992[73]—3 of 17 patients developed RBD, Patient 12, Nortriptyline, 100 mg/day; Patient 13, Imipramine, 225 mg/day; Patient 14, Imipramine, 30 mg/day				
• Tricyclic antidepressant	• Patient 12: Methylphenidate 35 mg/day • Patient 13: Methylphenidate 110 mg/day • Patient 14: Pemoline 112 mg/day	3, mean age 41, 1 male No	Yes. 10/17 had PLMS. Unknown if patient 12, 13, 14 had PLMS.	Narcolepsy
• Various • Unknown	• None	No No	Sleep disordered breathing not mentioned	Yes

Table 3 continued on following page

Table 3 *(continued)*

Schenck et al. 1992[28]—SSRI: fluoxetine TCAs: amitriptyline, nortriptyline, imipramine, desipramine, protriptyline, trimipramine				
• SSRI • TCA	• 2 patients with subclinical RBD on TCA: imipramine • Others unknown	Total patients unknown Mean age unknown Sex distribution unknown 41 patients on fluoxetine 52 patients on TCA (amitriptyline 23, nortriptyline 8, imipramine 10, desipramine 6, protriptyline 4, trimipramine 1) One patient with RBD on fluoxetine: 32-year-old man Two patients with subclinical RBD on TCA: 32-year-old woman, 37-year-old man Other patients unknown	Yes. 15/41 patient on fluoxetine 13/52 patients on TCA Unknown whether patients with RBD or subclinical RBD had PLMS Mean age across all groups: 38	Psychiatric
		No		
• Various medications	• 1 patient with RBD on fluoxetine: cessation of fluoxetine → failed	No	Yes 16/41 patients on fluoxetine 21/52 patients on TCA Unknown whether patients with RBD or subclinical RBD had OSA	Yes
• 1 patient with RBD on fluoxetine: fluoxetine 20 mg BID • 6 patients with subclinical RBD on fluoxetine: unknown • 1 patients with RBD on TCA: unknown • 150 mg at bedtime		No		
Niiyama et al. 1993[54]—Clomipramine, 50 mg/day				
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• Unknown	11, mean age 20, all male	PLMS not mentioned	Normal
		No		
• 19-37 h, 2-6 h	• None	No	Sleep disordered breathing not mentioned	No
• 1 h before PSG		No		
Louden et al. 1995[57]—Selegiline, Patient 1, 5 mg/day; Patient 2-3, 10 mg/day				
• Monoamine oxidase type B inhibitor	• Patient 1: unknown • Patient 2: Carbidopa 25 mg/levodopa 100 mg BID, other medications unknown • Patient 3: unknown	Three patients Patient 1: 81, male Patient 2: 60, male Patient 3: 71, female Mean age: 70	PLMS not mentioned.	Parkinson disease
		No		
• Unknown	• Patient 1: not evaluated • Patient 2: Discontinuation of selegiline → RBD ceased • Patient 3: not evaluated	No	Sleep disordered breathing not mentioned.	Yes
• Patient 1: unknown • Patient 2-3: twice a day		No		
Carlander et al. 1996*[77]—Experimental acetylcholinesterase inhibitor				
• Acetylcholinesterase inhibitor	• Unknown	1, 66, male	PLMS not mentioned	Alzheimer's disease
		No		
• Unknown	• Discontinuation of experimental acetylcholinesterase inhibitor → RBD subsided	No	Sleep disordered breathing not mentioned	Yes
• Unknown		No		
Schutte et al. 1996*[58]—Venlafaxine, dosage unknown				
• Serotonin reuptake inhibitor • Norepinephrine reuptake inhibitor • Dopamine reuptake inhibitor	• lithium, lovastatin	1, 59, male	PLMI: 17.	Psychiatric
		No		
• 5 h, 2 h	• Addition of clonazepam → RBD ceased	No	Patient on CPAP during PSG after start of venlafaxine. Prior PSG showed AHI of 46.	Yes
• Unknown		No		

Table 3 continued on following page

Table 3 *(continued)*

Iranzo et al. 1999[78]—Bisoprolol, Patient 1, 10 mg/day; Patient 2, 2.5 mg/day				
• β -adrenoreceptor antagonist	• Unknown	Patient 1: 50, female Patient 2: 56, male	PLMS not mentioned	Hypertension
		No		
• 9-12 h, 2-4 h	• Patient 1: Bisoprolol discontinued → RBD ceased • Patient 2: Bisoprolol replaced by enalapril → RBD subsided	No	Sleep disordered breathing not mentioned	Yes
• Unknown		No		
Attarian et al. 2000[55]—Clomipramine, 75 mg/day				
• Tricyclic antidepressant • Inhibits re-uptake of serotonin	• Unknown	1, 55, female	PLMS not mentioned	Narcolepsy
		No		
• 19-37 h, 2-6 h	• None	No	Sleep disordered breathing not mentioned	Yes
• Bedtime		No		
Onofrj et al. 2003[59]—Mirtazapine, 30 mg/day				
• post-synaptic 5-HT_2 and 5-HT_3 antagonist	• Patient 1: 500 mg levodopa, benserazide • Patient 2: 300 mg levodopa and carbidopa • Patient 3: unknown • Patient 4: 600 mg levodopa and carbidopa, benserazide	4, mean age: 72, all male	PLMS not mentioned	Parkinson disease
		No		
• 20-40 h, 2 h	• Patients 1-4: Discontinuation of mirtazapine → RBD ceased	No	Sleep disordered breathing not mentioned	Yes
• Unknown		No		
Winkelman et al. 2004[29]—5 patients on fluoxetine, 25-50 mg/day; 3 patients on paroxetine, 15-40 mg/day; 3 patients on citalopram, 20-40 mg/day; 3 patients on sertraline, 100-225 mg/day; 1 patient on venlafaxine, 400 mg/day				
• SSRI	• 2 patients on bupropion • Other medications unknown	15, mean age 45, 6 male	PLMS not mentioned	Psychiatric
		No		
• Various	• None	No	Patients with OSA were excluded	No
• Unknown		No		
Dib et al. 2008[75]—12 patients. Serotonergic antidepressants were evaluated. Exact medications unknown.				
• SSRI	• Unknown	12, age range: 40-60, all male	PLMS not mentioned	Unknown
• Various	• None	No	Sleep disordered breathing not mentioned	Unknown. Tonic EMG activity was significantly more in drug group than in control group.
		No		
• Unknown		no		

*Reference is a published abstract (Carlander 1996, Schutte 1996).
TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; Subclinical RBD in Schenck 1992 is defined as increased electromyogram tone in REM with no specific clinical correlates; PLMI, periodic limb movement index; AHI, apnea hypopnea index; QID, four times a day; PLMS, Periodic limb movements of sleep; OSA, obstructive sleep apnea; TCA, tricyclic antidepressants; RSWA, REM sleep without atonia; Tmax, time to maximum serum concentration; T1/2, serum half-life.

Table 4—Data extraction of important criteria performed in the literature analysis.

Literature criteria	RLS articles	PLMS articles	RBD/RSWA articles
Abstract	1*	2	3
Peer-reviewed papers	31	4	6
Large retrospective study	4	3	3
Small case series	5	3	7
Case Report	23	0	4
Medication considered was taken in the evening or at bedtime	5	1	2
Other medications taken by patient's were listed	12	0	5
RLS evaluated (for PLMS articles)	NA	5	NA
RLS (or RBD/RSWA) subsided with reduction of medication dose	4	NA	0
RLS (or RBD/RSWA) subsided with withdrawal of medication	4	NA	1
RLS (or RBD/RSWA) ceased with reduction of medication dose	2	NA	0
RLS (or RBD/RSWA) ceased with withdrawal of medication	10	NA	4
No personal history of RLS prior to drug use was noted	13	NA	NA
Article specifically excluded the following:			
Tobacco use	2	0	0
Alcohol use	4	0	0
Excessive caffeine use	0	0	0
Elevated BUN/creatinine	14	1	NA
Low ferritin	9	1	NA
Peripheral neuropathy	4	0	NA
Pregnancy in women of childbearing age	0/11	NA	NA
For RLS articles: Endorsement of NIH RLS criteria identified			
4/4 NIH RLS criteria met	11	NA	NA
3/4 NIH RLS criteria met	4	NA	NA
2/4 NIH RLS criteria met	8	NA	NA
1/4 NIH RLS criteria met	5	NA	NA
0/4 NIH RLS criteria met	4	NA	NA
PSG excluding sleep disordered breathing was performed	3	1	1
PSG was used to document presence or absence of PLMS	9	6	3
For RBD/RSWA articles			
Clinical manifestations of RBD	NA	NA	10
Co-morbid psychiatric condition	NA	NA	4
Co-morbid narcolepsy condition	NA	NA	4
Co-morbid Parkinson's disease	NA	NA	2

NA, data not applicable; BUN, blood urea nitrogen; NIH, National Institutes of Health; PLMS, periodic limb movements in sleep; PSG, polysomnogram; RBD/RSWA, rapid eye movement (REM) behavior disorder/REM sleep without atonia; RLS, restless legs syndrome; *This abstract was a large retrospective study

Table 5—Drug-induced restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), and rapid eye movement behavior disorder/rem sleep without atonia (RBD/RSWA)

Drug	RLS		PLMS		RBD/RSWA	
Antidepressants: TCA	**Reference Name**	**Score**	**Reference Name**	**Score**	**Reference Name**	**Score**
Amitriptyline	Leutgeb 2002 [22]	10	Garvey 1987[24] Husain 1997[25]	9 8	Schenck, Mahowald, Kim 1992 [28]	8
Clomipramine	Myers 1986[31] Leutgeb 2002 [22]	8 10	NA	NA	Guilleminault 1976 [27] Besset 1978 [74] Bental 1979[72] Niiyama 1993[54] Attarian 2000[55]	10 7 4 7 5
Dibenzepine	Leutgeb 2002 [22]	10	NA	NA	NA	NA
Desipramine	NA	NA	Garvey 1987 [24]	9	Schenck, Mahowald, Kim 1992 [28]	8
Doxepine	Leutgeb 2002 [22]	10	NA	NA	NA	NA
Imipramine	Myers 1986[31] Leutgeb 2002 [22]	8 10	Ware 1984 [66] Garvey 1987 [24]	7 9	Schenck, Mahowald 1992 [73] Schenck, Mahowald, Kim 1992 [28]	6 8
Maprotiline	Leutgeb 2002 [22]	10	Garvey 1987[24]	9	NA	NA
Notriptyline	Myers 1986[31] Leutgeb 2002 [22]	8 10	Garvey 1987 [24]	9	Schenck, Mahowald 1992 [73] Schenck, Mahowald, Kim 1992[28]	6 8
Opipramol	Leutgeb 2002 [22]	10	NA	NA	NA	NA
Trimipramine	Leutgeb 2002 [22]	10	Ware 1984 [66]	7	Schenck, Mahowald, Kim 1992[28]	8
Antidepressants: SSRI						
Citalopram	Leutgeb 2002 [22]	10	Yang 2005 [26]	**15**	Winkelman 2004 [29]	7
Escitalopram	Page 2008 [51]	**14**	NA	NA	NA	NA
Fluoxetine	Bakshi 1996[34] Dimmit 2000[20] Leutgeb 2002 [22] Prospero-Garcia 2006 [52]	11 7 10 10	Dorsey 1996 [76] Husain 1997 [25] Yang 2005 [26]	8 8 15	Schenck, Mahowald, Kim 1992[28] Winkelman 2004 [29]	8 7
Paroxetine	Sanz-Fuentenebro 1996[35] Dimmit 2000 [20] Leutgeb 2002 [22] Ozturk 2006 [46]	11 7 10 8	Perroud 2007[48] Husain 1997 [25] Yang 2005 [26]	7 8 **15**	Winkelman 2004 [29]	7
Sertraline	Hargrave 1998 [36] Dimmit 2000 [20] Leutgeb 2002 [22]	4 7 10	Husain 1997 [25] Yang 2005 [26]	8 **15**	Winkelman 2004 [29]	7
Antidepressants: MAOI						
Phenelzine	NA	NA	NA	NA	Akindele 1970 [56]	8
Histamine antagonist						
Mianserin	Paik 1989[60] Hargrave 1998[36]	12 4	NA	NA	NA	NA
Antipsychotics: Typical						
Haloperidol	Horiguchi 1999 [37]	9	NA	NA	NA	NA

Table 5 continued on following page

Table 5 *(continued)*

Drug	RLS		PLMS		RBD/RSWA	
Antidepressants: Mixed mechanism	**Reference Name**	**Score**	**Reference Name**	**Score**	**Reference Name**	**Score**
Buproprione	NA	NA	Yang 2005 [26]	**15**	NA	NA
Mirtazapine	Bonnin 2000 [39] Agargun 2002 [40] Bahk 2002 [41] Chang 2006 [47] Prospero-Garcia 2006 [52]	7 9 10 11 10	NA	NA	Onofrj 2003 [59]	6
Trazadone	NA	NA	Garvey 1987 [24]	9	NA	NA
Venlafaxine	NA	NA	Salin-Pascual 1997 [53] Yang 2005 [26]	9 **15**	Schutte 1996 [58]	5
Antipsychotics: Atypical						
Olanzapine	Kraus 1999[38]	**14**	NA	NA	NA	NA
Risperidone	Wetter 2002 [42]	12	NA	NA	NA	NA
Antiepileptics						
Methosuximide	Drake 1988[63]	8	NA	NA	NA	NA
Phenytoin	Drake 1988[63]	8	NA	NA	NA	NA
Zonisamide	Chen 2003 [44]	12	NA	NA	NA	NA
Other						
Bisoprolol	NA	NA	NA	NA	Iranzo 1999 [78]	6
Cimetidine	O'Sullivan 1993 [33]	9	NA	NA	NA	NA
Lithium	Heiman 1986 [30] Terao 1991 [32]	5 6	NA	NA	NA	NA
L-thyroxine	Tan 2004 [45]	11	NA	NA	NA	NA
Pergolide and L-dopa/Carbidopa	Santamaria 2003 [43]	13	NA	NA	NA	NA
Selegiline	NA	NA	NA	NA	Louden 1995 [57]	**10**
Sodium oxybate	Abril 2007 [49]	13	NA	NA	NA	NA
Tramadol	Earley 2006 [68] Vertrugno 2007 [50]	6 **14**	NA	NA	NA	NA

References and evidence scores are listed for each medication (see methodology section for scoring guidelines). TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; NA, data not available. Bolded scores are the highest scores for RLS (14), PLMS (15), and RBD/RSWA (10).

Table 6—Medications with best evidence for inducing nocturnal events based on trials of medication reduction in dosage and withdrawal of medication and evidence scores (see methodology section for scoring guidelines)

RLS subsided with reduction of medication dose

Reference	Drug	Score
Paik 1989[60]	Mianserin	12
Kraus 1999[38]	**Olanzapine**	**14**
Chen 2003[44]	Zonisamide	12
Ozturk 2006[46]	Paroxetine	8

RLS ceased with reduction of medication dose

Reference	Drug	Score
Terao 1991[32]	Lithium	6
Markkula 1997[62]	Mianserin	8

RBD/RSWA subsided with withdrawal of medication

Reference	Drug	Score
Carlandar 1996[77], abstract	Experimental acetylcholinesterase inhibitor	4

RLS subsided with withdrawal of medication

Reference	Drug	Score
Drake 1988[63]	Phenytoin	8
Tan 2004[45]	L-thryoxine	11
Earley 2006[68]	Tramadol	6
Vetrugno 2007[50]	**Tramadol**	**14**
Page 2008[51]	**Escitalopram**	**14**

RLS ceased with withdrawal of medication

Reference	Drug	Score
Drake 1988[63]	Methosuximide	8
Bakshi 1996[34]	Fluoxetine	11
Markkula 1997[62]	Mianserin	8
Kraus 1999[38]	**Olanzapine**	**14**
Bonin 2000[39]	Mirtazapine	7
Bahk 2002[41]	Mirtazapine	10
Wetter 2002[42]	Risperidone	12
Santamaria 2003[43]	L-dopa, Pergolide	13
Chang 2006[47]	Mirtazapine	11

RBD/RSWA ceased with withdrawal of medication

Reference	Drug	Score
Akindele 1970[56]*	Phenelzine	8
Louden 1995[57]	**Selegiline**	**10**
Iranzo 1999[78]	Bisoprolol	6
Onofrj 2003[59]	Mirtazapine	6

None of the articles on periodic limb movements of sleep (PLMS) performed re-evaluation for PLMS at reduced dosage or off of medication. RLS, restless legs syndrome; RBD/RSWA, rapid eye movement (REM) behavior disorder/REM sleep without atonia. Bolded articles are one with the highest scores. *Polysomnogram performed after withdrawal of medication.

Table 7—Maximum scores based on article type

Article type	RLS article maximum score	PLMS article maximum score	RBD/RSWA article maximum score
Large retrospective study, published abstract	21	19	11
Small series, published abstract	20	18	10
Case report, published abstract	19	17	9
Large retrospective study, published paper	22	20	12
Small series, published paper	21	19	11
Caser report, published paper	20	18	10

PLMS, perioidic limb movements of sleep; RLS, restless legs syndrome; RBD/RSWA, rapid eye movement (REM) behavior disorder/REM sleep without atonia.