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Assessment of Change in Restless Legs Syndrome Symptoms during the Acute Drug-withdrawal Period

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1. INTRODUCTION

The standard treatment of restless legs syndrome (RLS) with dopaminergic (DA) agents is complicated by the eventual development of augmentation and the need for alternative therapy [1–6]. Part of the treatment for subjects augmented on DA agents is to taper down and off of the DA agent [6]. Clinical reports during the first several days off the DA agents indicate patients may experience severe sleep loss with worsening of RLS symptoms. This experience may result in the failure to get off the medication [7]. Despite the clinical report of these significant withdrawal problems, no prior study has prospectively evaluated daily symptoms during withdrawal of RLS medications after a standard dose tapering. In particular, it is not known if patients experience lower quality sleep and worse RLS symptoms coming off DA agents than coming off non-DA agents (eg, alpha-2 delta or opioid medications). In this study, daily clinical status, as well as periodic leg movements (PLM) while in bed, were assessed during an eight-night period in which patients were free of all RLS medications following a medication-tapering period. Considering the aforementioned clinical reports, we expect that during the post-taper withdrawal period (PTWP), those on DA agents will experience pronounced RLS symptom features, eg, sleep disruption (an indicator of RLS severity), PLMS, RLS symptom duration and intensity, that gradually improve. We expect those on non-DA agents will show little or no significant improvement in these symptom features over the PTWP.

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2. METHODS

2.1. Participants

All patients consented to a Johns Hopkins IRB-approved study in which withdrawal from RLS medications after a medication-tapering period was part of a larger protocol. The diagnosis of RLS was based on a Hopkins-Hening structured diagnostic interview [8] conducted by an RLS expert applying the current RLS diagnostic criteria [9]. These patients were then screened to ensure they had no indication for secondary causes of RLS and no other significant medical or psychiatric problems that would disrupt their sleep. The patients had to have regular nocturnal sleep patterns with no indication for sleep phase disturbance. Since transcranial magnetic stimulation was part of the study participants had to have well defined handedness and could not be highly skilled at hand motor tasks (eg, music, art). At the time of entry to the study, the patients had to be free of all psychoactive medications aside from RLS medications. Patients were required to be completely off all RLS medications for at least 10 days before entering the sleep lab for two consecutive nights. Patients were provided with a standardized dose-tapering schedule prior to stopping the RLS drugs. The drug-tapering period and the first eight nights and seven days of the post-tapering withdrawal period (PTWP) were completed at home prior to coming in for sleep lab evaluation. Many patients were traveling to the study site during the ninth and tenth days of the PTWP; therefore, only the first eight nights and seven days of the PTWP were used for analyses. This study evaluated only patients who enrolled in the parent study and who were taking only one RLS medication at the time of enrollment. Throughout the drug taper period, no patients dropped out. The patients included in the study had to have an average PLM/hr >15 as measured by leg activity monitors (PAM-RL) worn for the last five nights of the PTWP. They had to have no significant sleep-disordered breathing on the first night sleep lab evaluation (AHI<15/hr).

2.2. Medication withdrawal

A gradual dose tapering was made prior to stopping the medications. Those on pramipexole had a 0.25 mg dose decrease every three days. Those on ropinirole at doses < 1.0 mg had a 0.25 mg dose decrease every three days. Those on ropinirole doses greater than 1.0 mg were switched to pramipexole at a quarter of the ropinirole dose and then tapered following the same procedures for pramipexole. The pramipexole and ropinirole doses of 0.25 mg were stopped without dose tapering. Those on rotigotine had the dose decreased by 1 mg every five days. For the last step in rotigotine reduction, patients placed the patch on in the evening and took it off in the morning for five days, after which the drug was stopped. Gabapentin and opioid doses were decreased one therapeutic dose level (gabapentin 300 mg; oxycodone 5 mg) every three days.

During the medication-tapering period and subsequent PTWP, the research staff had one or more telephone contacts with the patients. These were to encourage the patient to both continue with the process and also wear the PAM-RL meters on the legs during each night of the PTWP. No patient dropped out from the study during either the medication-tapering period or PTWP.

2.3. Measurements of RLS severity

2.3.1 Subjective measures.—Changes in RLS severity over the PTWP were measured by changes in: 7-point global RLS severity scale (GRS), hours with RLS symptoms (HwRLS), total sleep time (TST), wake after sleep onset (WASO), nap minutes during the day and time-of-onset-of-RLS symptoms (TORLS). TORLS was adapted from a primary clinical measure used to define changes in RLS severity with RLS augmentation [10]. The patient made daily recordings of their hours of sleep and their hours with RLS symptoms using an RLS-sleep-wake (SW) log. The SW log was completed at night before going to bed and again in the morning on completion of their sleep-period [10]. Both sleep and RLS symptom hours were determined from the daily SW logs. The hours-with-sleep assessment was divided into (1) the primary sleep-period per individual report, which was usually between 21:00 to 09:00 for TST and WASO, and (2) the primary wake-period during which nap-times were assessed. For each patient, the first hour of RLS symptoms after 06:00 was recorded as the time-of-onset-of-RLS-symptoms (TORLS). If no RLS symptoms were reported that day, the time of sleep onset for the following night was substituted for analyses. TST and WASO were calculated from the patients' primary sleep periods, and HwRLS were calculated from each midnight (0:00) to the midnight of the next night. Only patients who had completed at least eight nights of their SW logs were included in the final analyses. TST, WASO, and GRS were recorded for each night, while nap time and TORLS were recorded for each daytime-period between the primary sleep-periods. Some patients traveled on the eighth day; consequently, HwRLS, nap time and TORLS were limited to seven days. Each morning at the conclusion of the individual's sleep period, the patient also completed a 7-point global RLS severity scale (GRS score), rating their RLS severity over the past 24-hours: 0-none, 1-minimal, 2-mild, 3, 4-moderate, 5, 6-severe RLS symptoms. Overall symptom severity was also assessed using the International Restless Legs Syndrome Study Group Severity Scale (IRLSS score) [11], immediately before medication tapering and on the eleventh day of the PTWP. These subjective measures were used to evaluate RLS severity in all patients.

2.3.2. Objective measures.—Patients wore a PAM-RL leg monitor (Phillips Respironics, Inc.) on each leg during their usual sleep period during the PTWP with only the first eight nights used in analysis. The PAM-RL monitor provides a validated measure of the periodic limb movements (PLM) while in bed, from which the PLM index (PLM per hour in bed) is derived [12]. The leg showing the greatest PLM index for a given night was used as the PLM index for that night. Polysomnographic (PSG) recordings were obtained on the 11th and 12th day of the PTWP using the AASM standard montage with six EEG, two EOG, chin EMG, and bilateral anterior tibialis EMG [13]. As there were no significant sleep apnea events on the first night (significant sleep apnea was an exclusion criteria), airflow, respiratory effort, and oxygen saturation were not included in the second night PSG. The PLM of sleep (PLMS), from which the PLMS index (PLMS per hour of sleep) was derived, were obtained from the second-night PSG using the standard 2006 WASM visual scoring rules [14].

2.4 Hypotheses and statistical analyses

In this study, we measured severity of RLS based on: increased hours with RLS symptoms, earlier onset in the day, increased disruption of sleep with increased sleep loss, and increased PLMS. The subjective report of hours with RLS and degree of sleep disruption are considered in the IRLS severity scale (items 7 and 4 respectively). Earlier onset of RLS is considered a primary measure of worsening RLS with dopamine RLS augmentation [9]. PLMS have been shown to correlate moderately well with the IRLS and Johns Hopkins RLS severity scales [15].

Based on these premises, three hypotheses were established *a priori* for this study. First, it was hypothesized that patients would show significant changes over the first eight nights and seven days of PTWP for subjective (TST, WASO, GRS score, total HwRLS, and time napping (minutes) per day (nap-time) and objective (PLM index based on PAMRL) measures of disease severity. As the DA agents may be at greater risk of inducing RLS-related withdrawal symptoms, our analysis was done separately for the DA-drug-withdrawal group (DA group) and non-DA-drug-withdrawal group (non-DA group). Changes in symptom measures were evaluated by single-factor (days) ANOVA for each drug group separately. The second hypothesis was that for the first day of the PTWP, the DA group compared to non-DA group would show features indicating more severe RLS based on subjective and objective measures of disease severity as noted above. Subjective measures were statistically evaluated in *a priori* determined hierarchical order for expected significant effect sizes as follows: TST, WASO, GRS score, total HwRLS, and time napping per day. Third, it was hypothesized that time of onset of RLS symptoms (TORLS), the primary sign of Dopamine augmentation, would be earlier for the DA group compared with the non-DA group on first day of PTWP. The premise for the second and third hypotheses is that the enhanced RLS-related withdrawal symptoms (increased intensity and earlier-onset) would be maximal within first few days of the PTWP and greater in DA-treated than in non-DA-treated patients.

Several exploratory analyses were made without correction for multiple testing. All the measures recorded during the PTWP were evaluated for differences between drug groups for each day of the PTWP using unequal variance t-tests. The daily scores for HwRLS in each of the four 6-hour time periods in the day were evaluated by single-factor ANOVA for significant changes over the eight day PTWP and by unequal variance t-tests for differences between drug groups on each day of the PTWP. The RLS severity measures measured on day one of the PTWP were tested within drug groups for correlation with age and for DA drug dose using the pramipexole dose equivalences of 5:1 ropinirole:pramipexole [16] and 3:1 rotigotine:pramipexole, [17]. The data for day one of the PTWP were also evaluated for significant differences between each of the three dopamine agonists, and these results may be found in the supplemental data.

A statistical significance of $p < 0.05$ was used for all ANOVA with two-tailed tests. One-tailed unequal variance t-tests were used for directional between-group hypotheses for each day. Statistical testing followed the ordered tests of primary hypotheses, provided that each prior test was significant. The exploratory analyses were designed to guide future studies, and analyses did not correct for multiple comparisons.

3. RESULTS

3.1. Subjects

There were 29 subjects who fit the inclusion criteria for this analysis: 24 on DA medications, and five on non-DA medications. The DA group was significantly older than the non-DA group (mean $\pm$ sd: 60.16 ± 8.72 vs. 49.00 ± 3.60 , $p = 0.0001$). There were no significant differences between the DA and non-DA groups for gender (66% vs. 80% female). The DA and non-DA groups' IRLS scores did not differ significantly while on treatment (mean $\pm$ sd: 20.38 ± 7.63 vs. 22.60 ± 8.50 , respectively) or on day 11 of the PTWP (mean $\pm$ sd: 26.26 ± 5.89 vs. 25.40 ± 8.56 , respectively). However, there was a significant increase in IRLS score for on compared to day 11 of medication for the DA group ($p = 0.002$), but not for the non-DA group. There were no significant differences between these groups for days of medication tapering before stopping drug and age of onset of RLS. Morning fasting serum ferritin levels were significantly higher in the DA group compared to non-DA group (mean $\pm$ sd: 48.37 ± 32.78 vs. 25.74 ± 17.55 $\mu\text{g/l}$, $p = 0.03$). There were no significant differences for transferrin saturations or iron levels between groups (Table 1). The number of patients on each specific drug and the mean and range of the doses are presented in Table 2.

3.2. Primary analyses of drug withdrawal effects

3.2.1 Analysis across the eight night, seven day PTWP of the primary indices of RLS severity—The DA group showed significant improvement in subjective measures of disease severity over the eight day PTWP for TST, WASO, GRS score, and HwRLS but no change for nap-time (Table 3; Figure 1a-e). The non-DA group showed no significant changes in any of the subjective measures over the eight day PTWP. By the last day and night of the PTWP, subjective responses were fairly similar between the two groups (Figure 1a-e). Analysis across the eight day PTWP found no change over time in PLM index for either group (Table 3).

3.2.2 Differences between groups on day one of the PTWP for the primary indices of RLS severity—On night one of PTWP, the DA group, compared to non-DA group, showed significantly lower TST (mean $\pm$ sd: DA, 2.75 ± 2.79 ; non-DA, 5.60 ± 1.82 ; $p = 0.0097$; Table 4). The TST for the first night of the PTWP for the DA group was 2 hours for 12 patients (50%) but 5 hours for six of the 25 patients (25%). WASO, which was next in hierarchical statistical design for subjective measures of severity, showed no group difference, and further testing of the primary hypotheses with the remaining primary subjective variables (GRS score, total HwRLS, and nap-time) was stopped according to hierarchical analysis. Exploratory analyses of day one and group-differences for the other primary subjective variables are given in Table 4 and in Figure 1. The PLM analysis, the primary objective measure of severity, showed a significantly greater PLM index for the DA group compared to non-DA group during the first night of the PTWP (mean $\pm$ sd: DA, 143.87 ± 130.02 ; non-DA, 27.61 ± 16.45 ; $p = 0.0001$; Table 4 and Figure 3).

3.2.3 Differences between groups in TORLS on first day of the PTWP—The TORLS for each group are presented for each of the seven days of the PTWP in Figure 2.

The DA group compared to the non-DA group had earlier TORLS, however the difference was not significant (mean $\pm$ sd: 13.67 ± 7.26 vs 17.40 ± 5.59 , $p = 0.12$, Figure 2).

3.3 Exploratory analyses of drug withdrawal effects

3.3.1 Analysis across the seven day PTWP for TORLS in each group—The DA group's average TORLS showed significant improvement over the eight day PTWP ($F = 2.21$, $p = 0.04$; Table 3; Figure 2). The average TORLS in the DA group improved from around 13:30 on day one of the PTWP to approximately 19:00 by the sixth day but reverted to about 14:00 on the seventh day. The non-DA group showed no significant changes over the eight day PTWP in TORLS (Table 3; Figure 2). There were no other significant differences between treatment groups in TORLS on any day of the PTWP (Figure 2).

3.3.2 Differences between DA and non-DA groups for each night of the PTWP

—Analysis for group-differences in PLM/hr found the PLM index to be significantly greater in the DA group compared to the non-DA group for each night of the PTWP (Figure 3). DA patients had significantly less TST than non-DA patients on the third night of the PTWP (Figure 1a) and significantly more nap time on days three and five of the PTWP (Figure 1e). The PSG, which was done on the twelfth day of the PTWP, showed similarly high average hourly rates of PLM during sleep for the DA group compared to the non-DA group (mean $\pm$ sd: 90.81 ± 58.94 vs. 24.73 ± 22.25 , $p = 0.00004$; Figure 3). From PSG data, significant differences were observed between both groups for two of the objective sleep measures, TST and WASO, on the 12th day of the PTWP (Table 6).

3.3.3 Analyses for age and dose effects on day one measures of severity

No significant correlation was found between the age of the subject and any sleep or RLS measure reported on day one of the PTWP (Table 5). Using a pramipexole-equivalent dose to establish a final DA dose used by a patient prior to the PTWP, a correlation was found between final DA-dose-equivalency and both TST and WASO (TST, $r = -0.51$, $p < 0.005$, WASO, $r = 0.48$, $p < 0.005$). Correlations between non-DA medication doses and sleep measures could not be calculated due to the lack of established dosage equivalence between the medications.

3.3.4 Separate set of analyses for each of the DA medications—After standardizing doses across the different types of DA agonists using an equivalent-dosing strategy, the mean dose-equivalency was significantly larger for pramipexole than for the other groups (pramipexole dose = 0.80 mg, ropinirole pramipexole equiv. = 0.47 mg, rotigotine pramipexole equiv. = 0.63 mg) (see supplemental material online for other analyses).

4. Discussion

Despite obvious limitations, particularly the small sample size of the patients not on DA, these data show a clear and interesting pattern of results: DA-treated patients showed significant withdrawal symptoms with profound sleep loss and persisting very high rates of PLMS. The non-DA treated patients showed no similar patterns, but this may be an artifact of the small sample size.

The DA-treated group showed clear signs of significant withdrawal during the PTWP. There were statistically significant improvements in both sleep (TST, WASO) and both amount and severity of RLS (HwRLS, GRS) over the eight night, seven day PTWP consistent with our primary hypothesis. However, it must be noted that there are no data on the sleep and RLS-specific measures for patients before drug taper. The PTWP RLS symptom improvement could indicate the patients were worse on- than off-treatment and the changes reflect improvement simply getting off the medication rather than a withdrawal effect. This seems very unlikely. The average IRLS is significantly worse off than on treatment (26 vs. 20). Moreover, the on-treatment IRLS of 20 is hardly severe enough to be compatible with the profound sleep loss (50% with TST 2 hours) and frequent RLS symptoms (1/3rd of the day) on the first PTWP withdrawal day. Future studies should, however, record the “baseline” values of these measures while patients are still on treatment for comparison with those recorded during PTWP.

During the PTWP three of the 24 DA patients (12.5%) had persisting low TST (<4 hours) for all but one night during the PTWP. It is unclear whether this reflected a more severe RLS status or if a longer duration off medications was needed for improvement. Nonetheless, patients discontinuing these DA treatments can overall be reassured that the profound sleep loss they experience at the start of the PTWP will generally recover by nights four or five off DA treatment.

Non-DA patients had no significant changes over the PTWP for any observed measures of RLS severity. There was no apparent profound sleep loss after dose taper: their average sleep time on night one of the PTWP was about 5.5 hours approximating that reported for untreated RLS [17]. The data show no indication of notable sleep loss or increased RLS symptoms during PTWP for these patients on non-DA drugs. A larger non-DA group, possibly treated with higher doses than those in this sample, may well show more indications for significant withdrawal, but there is certainly no indication for that from these data.

Finally, the average PLM index of these DA-treated patients were much greater than that of the non-DA treated patients on the first day (mean $\pm$ sd: 143.87 ± 130.02 vs. 28.41 ± 13.14 , $p = 0.0001$) and remained so over the eight night PTWP (Figure 3) and the 12th night as well (mean $\pm$ sd: 85.10 ± 54.41 vs. 23.40 ± 25.92 , $p = 0.0019$). In contrast, most prior studies of untreated RLS patients report about 40–50 PLMS/hr [19, 20]. For the DA group, the severity in this study of the RLS off medication was slightly higher (mean $\pm$ sd: IRLS = 26 ± 6) than that reported in the prior PSG studies (mean $\pm$ sd: 23 ± 4) [19], but this discrepancy seems inadequate to explain PLMS differences. These high PLMS rates might be expected after withdrawal from DA drugs that are known to be particularly good at suppressing PLMS [19, 20], but some improvement would be expected over the first eight nights of the PTWP. No such improvement was observed. As such, there is a troubling possibility that long-term dopamine treatment may lead to a profound increase in PLMS persisting for some time. Unfortunately, this study did not check the PLMS rates before the PTWP, so it is unclear if these rates would have been high on treatment and either remained high or became even higher off treatment. Given the close relation between dopamine treatment and RLS this

finding raises some disturbing concerns about persisting effects of long-term DA treatment on the dopaminergic system. Clearly, this deserves to be further evaluated.

There were some limitations to this study due to the methodologies and size of the study. First, no measures were recorded prior to or during the drug taper period. Next, these are small sample sizes, especially for the five non-DA treated patients. The finding of no significant withdrawal for the non-DA group must be accepted with great caution and may not apply to all groups and doses of non-DA treated patients. It should be noted that methadone was not one of the non-DA treatments, and no statements can be made from these data about withdrawal from methadone treatment of RLS. The combining of various drug treatments into the DA and non-DA treatment groups is another weakness of the study. Nevertheless, it seems that the withdrawal from any of these DA treatments is likely to have the same two-five nights of profound sleep loss during the PTWP. We do not know what sleep loss may occur during the drug taper period and are unable to comment on other RLS withdrawal symptoms.

Despite these limitations, this study demonstrates the course of the DA treatment withdrawal process after tapering of drug treatment. The initial sleep loss after the tapering and withdrawal of DA treatment raise some concerns about possible development of DA dependence with long-term treatment; however, this sleep disruption after drug-taper, while intense for some, is relatively time limited. By four-five days off the medication, patients may experience a return to expected RLS-related symptom levels for the severity of their RLS, except for the persistently high PLMS rates. Some patients, however, may seek to continue or increase their DA treatment doses to avoid the RLS-related withdrawal symptoms, particularly the profound sleep loss.

5. Conclusions:

This study provides a unique data set on the DA treatment withdrawal process. Despite the limitations of methodology and a small non-DA patient group, there are important observations to be made on the severity of and change in RLS-related withdrawal symptoms during the PTWP. RLS patients treated with DA agonists displayed severe sleep loss, even after the dose was gradually decreased prior to full withdrawal. In these patients, the PTWP included a profound loss of sleep with 50% having < 2 hours of sleep for the first night of the PTWP. After four-five nights, sleep time for most DA patients recovered to about the average symptom levels for untreated RLS. This profound insomnia indicates these patients may choose to return to the DA treatment rather than face another sleepless night. No similar problem was observed for the non-DA treated RLS patients, but a larger group of non-DA patients must be followed in future studies. Future studies should consider observing RLS severity measures in the drug-taper period and the pre-taper period. There is also some concern about long-term DA treatment resulting in high rates of PLMS that seemingly did not recover after discontinuing the DA drug. This may reflect some longer term effects on the dopaminergic system. Overall, the data indicate very poor sleep with marked RLS severity during the PTWP from DA medications and raise concerns about difficulty withdrawing RLS patients from DA treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*. 1996;19:205–13. [PubMed: 8723377]
- [2]. Tzonova D, Larrosa O, Calvo E, Granizo JJ, Williams AM, de la Llave Y, et al. Breakthrough symptoms during the daytime in patients with restless legs syndrome (Willis-Ekbom disease). *Sleep Med*. 2012;13:151–5. [PubMed: 22281003]
- [3]. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelmann JW, Earley CJ, Hogl B, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med*. 2013;14:675–84. [PubMed: 23859128]
- [4]. Garcia-Borreguero D, Benitez A, Kohnen R, Allen R. Augmentation of restless leg syndrome (Willis-Ekbom disease) during long-term dopaminergic treatment. *Postgrad Med*. 2015;127:71625.
- [5]. Garcia-Borreguero D, Silber MH, Winkelmann JW, Hogl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med*. 2016;21:1–11. [PubMed: 27448465]
- [6]. Kurlan R, Rabin M. Augmentation in restless legs syndrome: poor response to sudden withdrawal of dopaminergic therapy. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013;3:49–52.
- [7]. Kurlan R, Richard IH, Deeley C. Medication tolerance and augmentation in restless legs syndrome: the need for drug class rotation. *J Gen Intern Med*. 2006;21:C1–4.
- [8]. Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. *Sleep Med*. 2008;9:283–9. [PubMed: 17644424]
- [9]. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelmann JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med*. 2014;15:860–73. [PubMed: 25023924]
- [10]. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4:101–19. [PubMed: 14592341]
- [11]. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. 2003;4:121–32. [PubMed: 14592342]
- [12]. Sforza E, Johannes M, Claudio B. The PAM-RL ambulatory device for detection of periodic leg movements: a validation study. *Sleep Med*. 2005;6:407–13. [PubMed: 16139771]
- [13]. Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, et al. The AASM Manual for the Scoring of Sleep and Associated Events, version 2.3. Chicago: American Academy of Sleep Medicine; 2017.
- [14]. Zucconi M, Ferri R, Allen R, Baier PC, Bruni O, Chokroverty S, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med*. 2006;7:175–83. [PubMed: 16459136]

- [15]. Garcia-Borreguero D, Larrosa O, de la Llave Y, Jose Granizo J, Allen R. Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. *Sleep Medicine*. 2004;5:561–5. [PubMed: 15511702]
- [16]. Hobson DE, Pourcher E, Martin WR. Ropinirole and pramipexole, the new agonists. *Can J Neurol Sci*. 1999;26 Suppl 2:S27–33.
- [17]. Smith C Levodopa Dose Equivalency: A Systemtic Review. Univserity of Birgmingham: Birmingham Clinical Trials Unite; 2010.
- [18]. Allen RP, Stillman P, Myers AJ. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: Prevalence and characteristics. *Sleep Med*. 2010;11:31–7. [PubMed: 19464949]
- [19]. Partinen M, Hirvonen K, Jama L, Alakuijala A, Hublin C, Tamminen I, et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: A polysomnographic dose-finding study- The PRELUDE study. *Sleep Med*. 2006;7:407–14. [PubMed: 16815748]
- [20]. Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004;27:907–14. [PubMed: 15453549]

Highlights

- Withdrawal of DA agonists is associated with an acute insomnia
- Withdrawal from non-DA therapy produced no apparent sleep loss
- After withdrawal from DA agonist, PLM were sustained at very high rates
- RLS improves over the first four to five days following DA agonists withdrawal

a.

b.

c.

d.

e.

Figure 1.

Subjective measures (shown as means with standard error bars): Comparison between dopaminergic (DA) and non-dopaminergic (non-DA) treated groups during the eight night, seven day, post-taper withdrawal period (PTWP) for (a) total hours of sleep (TST) per night, (b) hours of wake after sleep onset (WASO) per night, (c) Global RLS Severity (GRS) score per day, (d) hours with RLS symptoms (HwRLS), and (e) minutes of napping per day. Results of t-test comparison between DA and non-DA is provided for each day when significant as: * $p<0.05$, ** $p<0.01$ without correction for multiple tests.

Figure 2.

Comparison between the dopaminergic (DA) and non-dopaminergic (non-DA) treated groups' times of onset of RLS symptoms (TORLS) (shown as means with standard error bars) each day after 6:00 over the seven days of the post-taper withdrawal period (PTWP). ANOVA showed significant improvement in TORLS over the PTWP for DA but not non-DA patients. No significant differences were found from t-test comparisons between DA and non-DA for any day without correction for multiple tests.

Figure 3.

Objective measure (shown as means with standard error bars): Comparison between dopaminergic (DA) and non-dopaminergic (non-DA) treated groups during the eight night post-taper withdrawal period (PTWP) for rate of periodic leg movements (PLM) per hour each night while in bed and rate of PLM during sleep (PLMS) per hour on the twelfth night based on PSG. Results of t-test comparisons between DA and non-DA is provided for each day when significant as: * $p < 0.05$, ** $p < 0.01$ without correction for multiple tests.

Table 1.

Pertinent study population information with comparisons between treatment groups.

Patient Demographics (n = 29)	DA (n = 24) Mean $\pm$ SD	Non-DA (n = 5) Mean $\pm$ SD	DA vs. Non-DA p-values
Age	59.62 $\pm$ 8.48	49.00 $\pm$ 3.60	0.0002**
Gender (F:M)	16:8	4:1	---
IRLS score (baseline on treatment, before titration)	20.38 $\pm$ 7.63	22.60 $\pm$ 8.50	0.3048
IRLS score (day 11 of PTWP)	26.26 $\pm$ 5.89	25.40 $\pm$ 8.56	0.4196
Drug Dosage (pramipexole equivalent, mg)	0.64 $\pm$ 0.43	---	---
Days of Titration	9.88 $\pm$ 8.46	6.20 $\pm$ 10.40	0.2456
Age of Onset	33.50 $\pm$ 16.41	21.20 $\pm$ 16.93	0.0953
Iron Fasting AM Blood Level (μ g/dl)	86.21 $\pm$ 32.51	71.00 $\pm$ 21.32	0.1124
Ferritin (ng/ml)	48.37 $\pm$ 32.78	25.74 $\pm$ 17.55	0.0293*
Transferrin Saturation (%)	28.00 $\pm$ 10.94	24.80 $\pm$ 12.83	0.3139
	DA (n = 24) p-value	Non-DA (n = 5) p-value	
IRLS Score Comparison (baseline vs. day 11 of PTWP)	0.0024**	0.3089	

Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

* Significant correlation, $p < 0.05$ and $p < 0.01$, respectively.

** Significant correlation, $p < 0.05$ and $p < 0.01$, respectively.

Table 2.

List of medications with dosage information and pramipexole-equivalency for dopamine agonists

Drug	Number	Dose Range (mg)	Average Dose (mg)	Pramipexole Equivalent Dose Range (mg)	Pramipexole Equivalent Average Dose (mg)
Pramipexole	8	0.25–1.5	0.91	0.25–1.50	0.91
Ropinirole	12	0.25–3.0	2.02	0.05–0.60	0.47
Rotigotine	4	2.0–3.0	2.25	0.67–1.00	0.75
Oxycodone	2	5–40	22.5	---	---
Gabapentin	3	300–600	400	---	---

Table 3.

ANOVA for change across the 8-day post-taper withdrawal period in primary measures of severity for each group.

Drug group	DA (n = 24)			Non-DA (n=5)		
	F	F _{crit}	p-value	F	F _{crit}	p-value
Total sleep time (TST), df = 7	2.864	2.060	0.007**	0.216	2.313	0.979
Wake after sleep onset (WASO), df = 7	3.156	2.060	0.003**	0.386	2.313	0.903
Global RLS severity (GRS) score, df = 7	3.372	2.062	0.002**	0.169	2.442	0.989
Total hours with RLS symptoms per day (HwRLS), df = 6	2.738	2.155	0.015*	0.400	2.445	0.873
Time napping per day, df = 6	0.336	2.155	0.917	0.146	2.445	0.988
Periodic leg movements (PLM) index, df = 7	0.399	2.060	0.902	0.206	2.313	0.982
Time of onset of RLS symptoms (TORLS), df = 6	2.212	2.155	0.044*	0.140	2.445	0.990

Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

For **Global RLS severity score**, n = 23 for DA group and n = 4 for the non-DA group. PLM and TORLS not included in hierarchical testing.

* Significant correlation, $p < 0.05$ and $p < 0.01$, respectively.

** Significant correlation, $p < 0.05$ and $p < 0.01$, respectively.

Table 4.

Comparison between groups on measures of RLS severity on first day of the post-taper withdrawal period.

	Mean $\pm$ SD		<i>p</i> -value for t-test
	DA (n = 24)	Non-DA (n = 5)	Hierarchical testing
Total sleep time (hours) (TST)	2.75 $\pm$ 2.79	5.60 $\pm$ 1.82	0.0097 **
Wake after sleep onset (hours) (WASO)	5.42 $\pm$ 2.93	2.90 $\pm$ 3.11	0.08
Global RLS severity score (GRS)	4.52 $\pm$ 1.47	3.75 $\pm$ 2.06	*** (0.26)
Total hours with RLS symptoms per day (HwRLS)	8.29 $\pm$ 5.85	6.80 $\pm$ 5.50	*** (0.30)
Time napping (minutes) per day	23.83 $\pm$ 40.47	1.60 $\pm$ 3.58	*** (0.007)
Periodic leg movements (PLM) per hour	143.87 $\pm$ 130.02	27.61 $\pm$ 16.45	0.0001 **
Time of Onset of RLS Symptoms (TORLS) (hour of day)	13.67 $\pm$ 7.26	17.40 $\pm$ 5.59	0.12

Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

PLM index and TORLS not included in hierarchal testing.

* Significant differences, $p < 0.05$ and $p < 0.01$, respectively.

** Significant differences, $p < 0.05$ and $p < 0.01$, respectively.

*** Hierarchical testing procedure halted after WASO measure. The p-values in parentheses are exploratory analyses but are considered non-significant since testing was stopped at WASO.

Table 5:

Correlation of measures of disease severity found on day 1 of the post-taper withdrawal period with age and with dose (pramipexole equivalents) for each drug class, dopaminergic (DA) and non-dopaminergic (non-DA).

	Age		Dose	
	DA (n = 24)	Non-DA (n = 5)	DA (n = 24)	Non-DA (n=5)
Total sleep time (hours)	0.1375	-0.3817	-0.5071 *	N/a
Wake after sleep onset (hours)	-0.1948	0.1560	0.4790 *	N/a
Global RLS severity score	-0.1012	0.5374	0.1942	N/a
Total hours with RLS symptoms per day	-0.0818	0.3533	0.2859	N/a
Time napping (minutes) per day	-0.1174	0.6202	0.1277	N/a
Periodic leg movements per hour	0.0787	-0.6669	0.0269	N/a

Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

* Significant correlation, $p < 0.05$ (DA, $df = 22$, critical value = 0.344; non-DA, $df = 3$, critical value = 0.805)

Table 6:

PSG sleep measures on the 12th day of the post-taper withdrawal period.

	Mean $\pm$ SD		<i>p</i> -value
	DA (n = 24)	Non-DA (n = 5)	
Total sleep time (hours)	5.58 $\pm$ 1.73	7.42 $\pm$ 0.20	0.000016 ^{**}
Wake after sleep onset (hours)	1.96 $\pm$ 1.38	0.47 $\pm$ 0.24	0.000018 ^{**}

Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

One non-DA patient had the PSG recorded on the 10th day of withdrawal. Abbreviations: dopamine-drug withdrawal (DA) and non-dopamine-drug withdrawal (Non-DA) groups.

^{**} Significant correlation, $p < 0.01$