Dopaminergic treatment in idiopathic restless legs syndrome: effects on subjective sleepiness

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**Abstract:**

**Objectives**

To assess frequency and characteristics of excessive daytime sleepiness (EDS) in restless legs syndrome (RLS) and the evolution of EDS under different RLS therapies.

**Methods**

We analyzed data from the “Swiss RLS” study, which was conducted to compare treatment efficacy and safety of the dopamine agonist pramipexole (PPX) versus levodopa/ benserazide (L/B) in de novo patients with idiopathic RLS and was performed as a randomized, double-dummy, comparative crossover trial. Primary outcome measure of the present study was the change in subjective sleepiness (as measured by Epworth sleepiness scale [ESS] score). There were thirty-seven patients (21 women) included, mean age was 56.6 (range 25-85), mean body-mass-index was 24.6 (+/-3.5 SD).

**Results**

At baseline, EDS (as determined by an ESS score >10), was found in 32% of the patients. Sleepy RLS patients were younger (p<0.001) than non-sleepy patients. PPX and L/B both were effective in the treatment of RLS symptoms (IRLS score, p<0.001 and p=0.002). Overall ESS was reduced (main effect for “time”, p=0.02) independent from the dopaminergic substance. In 5/37 patients ESS score deteriorated to >10 under treatment (PPX=3 patients, L/B=2 patients). No sleep attacks occurred.

**Conclusions:**

Excessive daytime sleepiness is frequent in RLS patients. Dopaminergic treatment usually promotes wakefulness, but infrequently leads to daytime sleepiness.

**Keywords:**

Restless legs syndrome; excessive daytime sleepiness; pramipexole; levodopa; Epworth sleepiness scale
**Introduction:**

Restless legs syndrome (RLS) is a frequent neurological disorder and one of the most common sleep disorders. Four essential criteria are obligatory for the clinical diagnosis. These criteria were established, and revised, by the International RLS Study Group.\(^1\) Due to RLS symptoms and/or PLM initiating and maintaining sleep is often complicated and disrupted. Whereas insomnia is a common complain in RLS little is known about the existence of excessive daytime sleepiness (EDS). In a few studies\(^2\)\(^4\) a subpopulation of RLS patients with daytime sleepiness (Epworth sleepiness scale [ESS]\(^5\) score >10) has been identified. Pathophysiology and predictors of EDS in RLS still remain unclear and there is little information on the evolution of EDS under different RLS therapies.\(^6\)\(^8\) Occasionally, sleep attacks are reported under dopaminergic treatment in Parkinson’s disease and RLS patients.\(^7\) Hence we analyzed data from the Swiss RLS (SRLS) trial (Bassetti et al., submitted), a randomized double-blind two-sequence, two-period crossover study which was conducted to determine the hypothesis of non-inferiority of pramipexole compared to dual-release,\(^9\) a combination of immediate- and slow-release, levodopa/benserazide (L/B) in the short-term treatment of RLS, in order to assess frequency and characteristics of RLS patients with EDS and to evaluate the course of EDS under adequate treatment with pramipexole (PPX) or L/B.

**Material and Methods:**

*Ethical aspects*

The protocol, patient information and informed consent has been reviewed and approved by the Institutional Review Boards (IRB) and has been notified to the Swiss Health Authority.

*Study design*

We analyzed data from the SRLS study. This study was conducted to compare non-inferiority of pramipexole versus levodopa in the treatment efficacy of RLS symptoms and PLM-S as multi-center, randomized, double-blind, comparative crossover trial with two treatment
periods of each four weeks. After treatment period 1 with either PPX or L/B, patients were switched to the respective other treatment (period 2). Cross-over washout period between treatments lasted two weeks.

Medication

PPX 0.25-0.75 mg (Mirapex/ Sifrol®) and dual-release L/B 125-375 mg (Madopar® DR) were administered orally, once daily before bedtime. Drug exposure for each period was 26 to 30 days, the washout period in between treatment periods lasted 2 weeks. There was no evidence of any carry-over effect.

Patient population

Patients aged 25 to 85 years, fulfilling all clinical criteria for diagnosis of idiopathic RLS, presenting RLS symptoms almost every day and with more than five PLM/h during bedtime were included. Patients previously treated with PPX, L/B or another DA, significant diseases other than restless legs syndrome, in particular other sleep-wake disorders, were excluded.

Outcome measures

Primary endpoint of the present study was the change in ESS score under treatment. Secondary outcome measures were efficacy in changes of RLS-score, PLMS index, sleep quality, and Hospital Anxiety and Depression Scale (HAD). PLMS index was determined using The PAM-RL Monitor System (IM Systems, Baltimore, USA). ¹⁰

Statistics

We analyzed data from 37 patients (21 women) with a complete data set. Excessive daytime sleepiness was defined as an ESS score >10. Statistical analysis was performed using SPSS software package version 14, SPSS Inc., Chicago, IL. Significant changes of ESS and IRLS under different treatments were estimated by 2-way and 3-way repeated measures analysis of variance (rANOVA, general linear model) with the between-subject factors treatment (pramipexole vs. levodopa), group (sleepy vs. non-sleepy patients) and the within factor time (baseline- end) followed by post-hoc t-tests. The chi-square and Student t-tests were used to
analyze categorical and continuous variables. Pearson’s product correlations were performed to identify correlations between the individual items. Significance was determined as \( p \leq 0.05 \). All results are expressed as mean (+ standard deviation).

**Results:**

*See Figure 1*

**Daytime sleepiness**

**Period 1:** We found an ESS >10 (mean 13.3 ± 2.1) in 12 (32%) and severe EDS, as determined by an ESS >14 in 5 (14% of all 37) patients. ESS was reduced with treatment in sleepy and non-sleep patients (main effect for “time” \( F_{1/33} = 6.63 \ p=0.02 \) independent from substance (period x treatment interaction: \( F_{1/33}=0.5, \ p=0.82 \). Triple interaction however revealed that the effect of treatment differed among the two groups (time x group x treatment interaction: \( F_{1/33}=4.3, \ p=0.05 \). In sleepy patients, pramipexole significantly improved ESS from 14.3 ± 2.3 to 10.5 ± 5.2 (n=6, \( p=0.05 \)), whereas under levodopa treatment ESS only slightly improved and statistically not significant from 12.3 ± 1.5 to 11 ± 2.8 (n=6, n.s.). In the non-sleepy patients, ESS did not significantly change (PPX: from 7.4 ± 2.2 to 8.1 ± 2.9, and L/B: from 6.0 ± 2.8 to 4.7 ± 1.6, respectively).

Under PPX (L/B) therapy in three (two) out of all 37 patients, ESS score deteriorated to a score >10. Nevertheless RLS symptoms (IRLS and PLMS) improved in these patients. No sleep attack occurred.

**Period 2:** We found 11 (30%) patients with ESS >10 (mean 12.5 ± 1.4) and one patient with ESS >14. In (all) sleepy patients, ESS improved under therapy (12.6 ± 1.4 to 11.2 ± 2.9, \( p=0.07 \)). Taking in account the different medications used, again there was no significant change of ESS under levodopa treatment 12.6 ± 1.6 to 12 ± 3 (n=8, n.s.) whereas in PPX there was an improvement of ESS from 12.3 ± 1.2 to 9 ± 2. Due to a too small number (n=3) of sleepy patients treated with pramipexole no statistical analysis was performed.
Differences and correlations: Sleepy RLS patients were younger than non-sleepy RLS patients (50.4 ± 7.5 versus 59.6 ± 11.6, p=0.007). No other statistical differences or correlations in gender, body mass index (BMI), medication, IRLS-score, depression, anxiety, or PLMS-Index were found between sleepy and non-sleepy RLS patients. For further details please see Table 1. None of the evaluated factors was able to predict the development of new sleepiness (on ESS).

Restless legs symptoms

Period 1: IRLS improved within period 1 (main effect of time: F 1/33=21.3, p=0.001) with either medication (no time x treatment interaction F1/33 = 0.1, p=0.9). Post hoc t-test confirmed that mean IRLS score of the 37 patients at baseline, was 22.8 ± 6.9 and improved to a mean of 15.4 ± 8.2 (p<0.001) under treatment with levodopa (n=17) or pramipexole (n=20).

The effect of pramipexole and levodopa on IRLS was quiet similar in sleepy and non-sleepy patients (time x group x treatment interaction: F 1/33=1.45, p=0.24). See Table 1.

Period 2: After cross-over at baseline of treatment period 2 mean IRLS for all patients was 18.8 (± 7.8) and improved to 15.3 (± 8.4), p=0.03.

Discussion:

To our best knowledge, this is the first study which tested for the evolution of EDS under two different dopaminergic RLS therapies (pramipexole and levodopa) in adequate dosing.

Among idiopathic RLS patients, EDS is estimated in a subgroup of 20-30%.2-4 Our result of 32% (period 1) and 30% (period 2), respectively, of sleepy RLS patients therefore is in line with previous studies.

From our results we could not identify major predictors of sleepiness in RLS patients. Sleepy RLS patients were younger, confirming the previous result of Bassetti et al.3 Besides of this, no statistical differences in respect to gender, severity of RLS (IRLS-score), body mass index...
(BMI), medication, depression, anxiety, or PLMS- Index were found when compared sleepy with non-sleepy patients.

Pramipexole and levodopa are both effective in the treatment of RLS symptoms. Overall ESS was reduced under dopaminergic treatment, mainly due to the reduction in sleepy patients. This finding is in contrast to Parkinson’s disease, where dopamine therapy often leads to daytime sleepiness. This difference is possibly due to different dosages and time of administration of the drugs.

Both treatments were of similar effect in the reduction of ESS with a trend in favor of PPX. Nevertheless in some patients ESS deteriorated and few patients became sleepy (ESS>10). This was the case for both treatments.

We assume that dopaminergic dysfunction is directly involved in excessive daytime sleepiness in RLS-patients. A dopaminergic dysfunction has also been suggested to be involved in EDS of other sleep disorders. Neurochemical studies have shown changes in dopamine metabolites concentrations in the CSF of patients with idiopathic hypersomnia (IH) and in patients with narcolepsy (N) suggesting an increased turnover or impaired dopamine release. Modafinil, a wakefulness-promoting drug, may increase wakefulness through activation of noradrenergic and dopaminergic systems. We hypothesize a dopaminergic dysfunction/ deficiency in sleepy RLS patients that differs from the pathophysiology of non-sleepy RLS patients, the exact mechanism of dopaminergic transmission affected in sleepy RLS patients however remains unclear. The different effects of levodopa and dopaminagonists on EDS however corroborate our assumption that the dopaminergic system has distinctive effects.

We are aware of the limitations of our study: analyses were done with only a small number of patients and the design of the study was done to evaluate treatment efficacy / non-inferiority of two treatments and not primary to evaluate excessive daytime sleepiness in RLS. Due to small numbers no intra-individual comparison after cross-over could be realized.
Further studies with greater populations including objective measurements (e.g. Multiple Sleep Latency Test) on sleepiness are needed to confirm our results.

Acknowledgements: The Swiss RLS study was founded by Boehringer-Ingelheim (Schweiz) GmbH.

References:


Figure legends

*Figure 1:* ESS distribution and evolution under dopaminergic treatment (treatment periods 1 and 2)
Table 1  Baseline PLMS index, demographic and clinical characteristics in RLS patients with and without excessive daytime sleepiness

<table>
<thead>
<tr>
<th></th>
<th>non-sleepy (ESS ≤10)</th>
<th>sleepy (ESS &gt;10)</th>
<th>p-value</th>
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<tr>
<td>n (%)</td>
<td>25 (68%)</td>
<td>12 (32%)</td>
<td></td>
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<tr>
<td>age [y]</td>
<td>59.6 (±11.6)</td>
<td>50.4 (±7.5)</td>
<td>0.007</td>
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<td>female sex, n (%)</td>
<td>14 (56%)</td>
<td>7 (58%)</td>
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<td>BMI</td>
<td>24.7 (±3.7)</td>
<td>24.5 (±3.5)</td>
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<tr>
<td>IRLS score</td>
<td>23 (±5.8)</td>
<td>22.7 (±6.9)</td>
<td>N.S.</td>
</tr>
<tr>
<td>PLM-S [/h]</td>
<td>21.3 (±14.6)</td>
<td>20.9 (±14.6)</td>
<td>N.S.</td>
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<tr>
<td>HADS, subscale anxiety</td>
<td>8.5 (±2.2)</td>
<td>8.6 (±2.3)</td>
<td>N.S.</td>
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<tr>
<td>HADS, subscale depression</td>
<td>11.3 (±1.3)</td>
<td>11.3 (±1.6)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

All results are expressed as mean (± standard deviation).

ESS: Epworth Sleepiness Scale  
BMI: Body-Mass-Index [kg/m²]  
IRLS: International RLS Study Group Rating Scale  
PLM-S: Periodic Leg Movements in Sleep  
HADS: Hospital Anxiety and Depression Scale