Poor effect of guideline based treatment of restless legs syndrome in clinical practice
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Poor effect of guideline based treatment of restless legs syndrome in clinical practice

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Abstract

*Background:* Numerous randomized controlled trials prove efficacy of dopaminergic and non-dopaminergic drugs in the treatment of restless legs syndrome (RLS). In contrast, epidemiological data demonstrate generally insufficient RLS treatment in clinical practice.

*Objective:* To prospectively assess the success of RLS treatment in the clinical setting and to evaluate potential demographical factors and comorbidities that may influence the response to therapy.

*Methods:* 100 patients with idiopathic RLS (40% had never received RLS specific treatment before) were examined at baseline and after 12 months. Recommendations for therapy according to RLS treatment guidelines of the German Neurological Society were given at baseline. Primary measures for the success of therapy were reduction of RLS symptoms (IRLS) and improvement of quality of life (RLS-QoL).

*Results:* No statistically significant improvement of IRLS and RLS-QoL could be detected after 12 months, neither in initially untreated nor in pre-treated patients. Poor treatment success, regarding improvement of RLS symptoms, quality of life and number of RLS related physician contacts, was related to the presence of neuropsychiatric comorbidity, i.e. somatoform disorders (prevalence 41%), chronic pain (32%), anxiety (20%) and major depression (16%).

*Conclusion:* Success of guideline conform treatment of RLS appears to be rather poor in clinical practice. Neuropsychiatric comorbidity may be a target for interventions to improve the overall outcome.
Introduction

With an age-dependent prevalence of about 10% in Germany, restless legs syndrome (RLS) is one of the most common neurological disorders. A number of randomized controlled trials have proven good efficacy and tolerability of various dopaminergic, opioid or antiepileptic drugs for the treatment of RLS symptoms (for current review see). Contrasting these findings, a number of epidemiological studies demonstrate a generally insufficient treatment of RLS symptoms in clinical practice. Beside the lack of the correct diagnosis, one explanation for these seemingly contradictory data might be that there are a number of comorbidities, regularly co-occurring in RLS, which may potentially impair treatment success, such as psychiatric disorders like depression or anxiety, pain disorders like fibromyalgia and migraine, iron deficiency as measured by low serum ferritin levels; excessive daytime sleepiness or cardiovascular disorders. Although a number of studies have been performed to elucidate factors that may be associated with RLS, to date no prospective data is available assessing and weighting all these factors in the clinical setting with regard to their impact on disease severity, quality of life and treatment success.

Here, we report the results of a 12-months prospective RLS benchmarking study aiming to assess (1) the effectiveness of guideline based RLS treatment on the improvement of RLS symptoms and quality of life apart from selected trial populations in a community based sample of 100 patients with idiopathic RLS and (2) to elucidate demographical factors and comorbidities which may influence the therapeutic outcome in the general clinical setting.

Patients and Methods

We included 100 consecutive patients with idiopathic RLS presenting for the first time in our outpatient department. Written informed consent was obtained from all patients, the study was approved by the local Ethics Committee. All patients had responded to a press article in the
two main regional newspapers searching for participants in a one year observational study to assess the course of idiopathic RLS. In total, 186 subjects had responded to the article, however 86 were excluded either for not having RLS (n=13), for having symptomatic RLS (n=46) or for seeking advice but not wishing to participate in a study (n=27).

All patients underwent a structured interview assessing demographical factors, RLS and treatment related symptoms and comorbidity (see below), as well as a thorough clinical and neurological examination by a RLS experienced neurologist. RLS diagnosis was confirmed using the RLS diagnostic index (RLS-DI) 18. Severity of RLS symptoms was assessed using the International RLS Study Group Rating Scale (IRLS) 19, quality of life was measured applying the RLS Quality of Life Questionnaire (RLS-Qol) 20. Based on the RLS guidelines of the German Neurological Society recommendations for further treatment and follow-up were given to the patients and the treating primary care physician in written form (figure 1). Patients were additionally educated about the background and course of the recommended treatment; expected improvements of RLS related symptoms and potential side effects in an open consultation of 30-60 minutes duration. After 12 months, a follow-up examination was performed including the same examinations as at baseline. Treatment and follow-up investigations between baseline and the 12 months follow up examination was performed as judged by the treating primary care physician.

Assessment of comorbidities

In an open consultation all patients were asked for comorbidities. Additionally, diseases which are known to be related to RLS were directly asked for in a structured interview (see introduction). Major depression and anxiety disorder were diagnosed according to DSM-IV criteria, somatoform disorders based on the German version of the Patient Health Questionnaire (PHQ) 21 and chronic pain according to ICD-10 criteria. Excessive daytime sleepiness was diagnosed according to the the ICD-10 criteria for hypsomnia. Diagnosis of
augmentation was based on the diagnostic criteria reported on the WASM consensus conference 2007 (Max-Planck–Criteria). Augmentation severity was assessed using the Augmentation severity rating scale (ASRS), depressive symptoms were rated with Beck’s depression inventory (BDI), daytime sleepiness was assessed using Epworth Sleepiness Scale (ESS).

Statistical analysis
For statistical analysis we used SPSS 17.0 (SPSS, Chicago, IL). As indicated in the introduction analysis was performed in two steps with regard to two different objectives.

(1)
Primary outcome measures for analysis of treatment success after 12 months were changes on IRLS and RLS-Qol (in absolute values as well as in percentages). Paired t-test for IRLS and RLS-Qol was performed for the whole cohort, as well as separately for pre-treated and initially untreated patients.

(2)
In order to identify demographical and disease related factors which may influence the clinical outcome, principal component analysis was performed for data reduction of 25 variables including demographical factors, comorbidities, measures of baseline symptom severity and treatment complications (see supplementary material for details). Five main components were extracted which accounted for 82% of the total variance in all variables. They are referred to as “age and somatic comorbidity”, “neuropsychiatric comorbidity”, “disease duration”, “augmentation” and “baseline disease severity”. Results were used as a basis for post-hoc subgroup analysis. Bonferoni correction for multiple comparisons was performed, results were assumed to be significant at p<0.05.
Results

Description of the cohort

An overview on demographics and outcome measures for the whole cohort as well as for the subgroups of pre-treated and untreated RLS patients is given in table 1. Comorbidities are listed in figure 2. At the time of the baseline examination 40% patients have never received RLS-specific treatment. Forty-two per cent of the patients had a monotherapy, 18% had a combined therapy for RLS symptoms. Guideline based therapy could be found in 64% of all patients at baseline. More detailed information on the medication is given in table 2. In 14% of the patients, baseline control of RLS symptoms was classified as sufficient by the examining neurologist. In all patients guideline based recommendations for optimization of RLS medication were given.

(1) Clinical outcome

Treatment course

During the 12 months observational period, the mean number of physician contacts for RLS was 3.1 ± 4.2, 42% had been referred to a neurologist by the primary care physician and 12% had been further referred to a tertiary care facility. In the follow-up examination after 12 months, guideline based treatment was achieved in 71% of the cases. In only three of the other patients non-guideline based advice was given by the treating primary care physician, in all other cases the patients reported to explicitly not follow the guideline-based recommendations. Reasons for non-compliance were given as follows: intent to spare medication (n=6), extreme fear of deterioration of RLS symptoms when reducing levodopa or changing from levodopa to another drug (n=5), general lack of belief in Western medicine (n=4), being afraid of side effects after reading the package insert (n=4), being afraid of drug dependency (n=3), hope for spontaneous improvement of symptoms (n=2), no specific reason
Demographical data and baseline IRLS, RLS-QoL, ESS and BDI did not differ between compliant and non-compliant patients.

41.2% of the treated patients experienced side effects. 11.8% of the patients experienced more than one side effect. However, in 86.1% side effects were rated as mild and did not lead to any change of the medication. The following side effects were observed: augmentation (24%), sleepiness (14.7%), nausea (13.2%), dizziness (8.8%), nocturnal compulsive eating (7.4%), headache (5.9%), vivid dreams (2.9%), leg edema (2.9%) and erectile dysfunction (1.5%).

**Treatment outcome**

As shown in table 1, IRLS and RLS-QoL did not improve after 12 months, neither regarding the whole cohort, nor in the subgroups of pre-treated patients, untreated patients, patients in whom guideline based treatment was achieved or non-compliant patients (p=0.13-0.32). Contrasting these findings, 91% of the patients receiving dopaminergic drugs, however, reported very good effectiveness of the applied drug in the reduction of the key RLS symptoms. Furthermore, treatment was rated satisfactory by the examiner in 40% of the cases, compared to 14% at baseline (p=0.002).

Regarding secondary outcome measures, ESS was unchanged after 12 months in the whole cohort (p=0.41) as well as in all subgroups (p=0.30-0.87). BDI improved significantly in the whole cohort (p=0.001), as well as in the subgroup of initially untreated patients (p=0.005), but not in any of the other subgroups (p=0.24-0.68).

**(2) Predictive factors**

As shown above neither initial treatment status nor compliance affected the therapeutic outcome. For assessment of other predictors of treatment success correlation analysis with regard to demographic factors, comorbidities, medication and side effects was performed including the whole cohort. No single factor was related to the improvement of IRLS or RLS-
QoL after 12 months (p=0.19-0.78). Principal component analysis for data reduction resulted in the extraction of five principal components as described above which were not correlated to each other. From these five principal components only “neuropsychiatric comorbidity” was related to the therapeutic outcome. Higher factor scores on this component are coherent with a higher number of different psychiatric and psychosomatic symptoms.

Based on these data, in a post hoc analysis we compared patients affected by neuropsychiatric comorbidity (NP+; n=64) and those free of neuropsychiatric comorbidity (NP-; n=36). There was no difference between both groups regarding demographical data (p=0.13-0.58) and baseline IRLS, RLS-QoL, ESS and BDI (p=0.08-0.58; table 1). During the 12 months observational period, NP+ patients had significantly more physician contacts for RLS than NP- patients (p<0.001) and were more often referred to specialists (p=0.003). After 12 months, the NP- showed no improvements on IRLS (paired t-test; p=0.35) and RLS-QoL (p=0.43), whereas the NP- group improved on both scales (p=0.005 and 0.008, respectively, see also figure 3). Neither group showed improvement on the BDI or ESS (p=0.13-0.69).

Discussion

This 12-months benchmarking study was set out to evaluate success of guideline based RLS treatment in the clinical setting and further to illuminate factors which may influence the therapeutic outcome.

Surprisingly, in this large cohort of 100 patients with idiopathic RLS neither symptom severity nor quality of life improved after 12 months of guideline based RLS treatment. This finding contrasts evidence from pharmacological studies demonstrating efficacy of various dopaminergic and non-dopaminergic drugs in the reduction of RLS symptoms and in the improvement of quality of life. However, it is line with data from large population based studies showing that in the general population RLS is rarely diagnosed and often insufficiently treated.
It has been stated that awareness and training of the treating physicians may be one of the most important issues to explain this apparent discrepancy. This is, however, not supported by our data demonstrating that (1) treatment according to the current therapy guidelines was achieved in 64% (baseline) and 71% (follow-up) of the patients, that (2) the vast majority of the patients not receiving guideline-based treatment was non-compliant despite good clinical advice by different physicians and that (3) compliance had no significant impact on the treatment outcome, anyway. Also demographical factors such as age, gender, age at symptom onset and disease duration as well as somatic comorbidities, specific drugs and side effects could be excluded as main causes for the poor treatment outcome in this cohort. Finally, even patients who received RLS medication for the first time did not significantly improve regarding RLS symptoms and quality of life. However, it needs to be considered that the expected striking effect of initiation of drug treatment may have not been displayed in our study because of the relatively long observational interval of 12 months. This emphasizes the need for long-term controlled studies to assess effectiveness of drug therapies in RLS.

According to our data, neuropsychiatric comorbidity is a major issue in the management of RLS patients. Neuropsychiatric comorbidity including anxiety, depression, chronic pain and various somatoform disorders is common in idiopathic RLS, affecting 64% of the patients in our cohort. As shown in figure 3, only a minority of these patients achieved improvement of RLS symptoms or quality of life, compared to about 80% of RLS patients without apparent neuropsychiatric comorbidity. Furthermore, neuropsychiatric comorbidity was the main predictor for a high number of RLS related physician contacts during the observational period. One reason for both, the poor outcome on objective scales and the high number of RLS related physician contacts may be that patients may not be capable to differentiate the key RLS symptoms from accompanying neuropsychiatric symptoms such as chronic pain and depression. These, however, obviously do cause a high degree of suffering, which is not
expected to change during RLS treatment, but might still be reflected in the symptom severity and quality of life scales. This assumption is supported by the finding that despite the poor outcome on the scales, still 91% of all patients reported excellent effectiveness of their RLS drugs. This interaction between neuropsychiatric comorbidity and improvement of RLS symptoms may also explain the contrasting results between pharmacological and epidemiological studies discussed above, since patients with predominant neuropsychiatric comorbidity were generally excluded from pharmacological trials. However, even when regarding only RLS patients without apparent neuropsychiatric comorbidity, the outcome in our study still appears poor with a mean improvement of IRLS of only 4.5 points and 3.8 points on RLS-QoL, although the majority did benefit from therapy.

Limitations

One may argue that the cohort examined in this study is a cohort of a tertiary referral center and might therefore be more severely affected by RLS and more difficult to treat than idiopathic RLS patients in the general population. However, to overcome this we recruited the patients from the general population via newspaper articles and did not include patients who had been referred to our clinic for diagnosis and treatment. Moreover, baseline symptom severity as measured by IRLS, RLS-QoL and distribution of age, sex and disease duration are in line with the description in population based cross-sectional studies, suggesting that our cohort does represent a normal cohort of idiopathic RLS patients.26 One may further argue that the cohort we examined was mixed regarding medication, what may bias the treatment outcome. From clinical experience, the greatest differences in the outcome would have been expected between pre-treated and initially untreated patients. The cohort examined is large enough to allow for differentiation of these two groups (n=60 vs. n=40, respectively); no differences in treatment success could be found comparing both groups. Moreover, this study was designed to monitor and quantify the treatment success in guideline based RLS treatment. All drugs applied according to the guidelines have already
shown efficacy in the reduction of RLS symptoms. The decision on a specific drug in clinical practice is individual and complex as it takes into account a number of factors such as expected side effects, comorbidity, concomitant medication, timely distribution of symptoms or even patient’s preference. Although this may cause some bias in the evaluation of treatment success, and the present study therefore does not fulfil the criteria normally applied to pharmacological trials regarding inter-individual comparability of the data, the rather large sample size (n=100) in this cohort should ensure that data is not biased to one specific drug. Finally, as described above there is no evidence in our data for a drug-specific positive or negative effect on the treatment success.

**Conclusion**

The findings in this RLS benchmarking study demonstrate for the first time that the success of RLS therapy in the clinical setting stays far behind the efficacy of drug therapy in pharmacological trials, although the medication seems to work equally well (91% excellent responses). Neuropsychiatric comorbidity including depression, anxiety, chronic pain and somatoform disorders seems to be a promising target for improvement of RLS treatment in clinical practice, since it does not only affect the majority of patients (64% in our cohort), but also appears to be the main predictor for frequent physician contacts and for poor treatment success most likely due to interfering neuropsychiatric symptoms. Therefore, careful consideration should be given to the diagnosis and treatment of neuropsychiatric comorbidities along with RLS in clinical practice. Future long term and controlled studies will have to address if and how supportive treatment strategies such as psychotherapy and behavioural treatment either as single or as add-on therapy may contribute to the success of RLS therapy. 27
Contributions

JG and DB designed the study. JG, NS and AKW were responsible for data acquisition and analysis. All authors contributed to the interpretation of the data. JG wrote up the manuscript, all authors contributed to the revision of the manuscript. DB supervised the study.

References


Table 1. Overview on the clinical data of baseline (BL) and follow-up (FU).

<table>
<thead>
<tr>
<th></th>
<th>RLS</th>
<th>Untreated</th>
<th>Pre-treated</th>
<th>p-value</th>
<th>NP-</th>
<th>NP+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographical data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>100</td>
<td>40</td>
<td>60</td>
<td>-/-</td>
<td>36</td>
<td>64</td>
<td>-/-</td>
</tr>
<tr>
<td>Age</td>
<td>61.6 ± 9.5</td>
<td>58.7 ± 7.7</td>
<td>63.5 ± 10.2</td>
<td>0.01</td>
<td>63.1 ± 8.0</td>
<td>60.8 ± 10.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender f:m</td>
<td>58:42</td>
<td>24:16</td>
<td>34:26</td>
<td>n.s.</td>
<td>23:13</td>
<td>35:29</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at symptom onset</td>
<td>36.4 ± 19.8</td>
<td>30.4 ± 20.8</td>
<td>40.4 ± 18.2</td>
<td>0.01</td>
<td>38.0 ± 20.1</td>
<td>35.6 ± 19.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Disease duration</td>
<td>24.0 ± 18.8</td>
<td>25.5 ± 20.6</td>
<td>23.0 ± 17.6</td>
<td>n.s.</td>
<td>25.0 ± 19.4</td>
<td>23.5 ± 18.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Family history</td>
<td>52%</td>
<td>45%</td>
<td>57%</td>
<td>n.s.</td>
<td>47%</td>
<td>55%</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Primary measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRLS (BL)</td>
<td>24.8 ± 8.2</td>
<td>23.3 ± 9.2</td>
<td>25.8 ± 7.4</td>
<td>n.s.</td>
<td>23.8 ± 8.3</td>
<td>25.4 ± 5.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>IRLS (FU)</td>
<td>23.7 ± 8.6</td>
<td>23.0 ± 8.9</td>
<td>24.2 ± 8.5</td>
<td>n.s.</td>
<td>19.3 ± 8.5</td>
<td>26.3 ± 7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IRLS (p-value)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td>0.005</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>RLS-Qol (BL)</td>
<td>32.0 ± 8.0</td>
<td>36.2 ± 9.5</td>
<td>30.4 ± 6.2</td>
<td>n.s.</td>
<td>37.4 ± 8.7</td>
<td>30.2 ± 7.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>RLS-Qol (FU)</td>
<td>32.4 ± 7.6</td>
<td>37.9 ± 10.2</td>
<td>30.5 ± 5.9</td>
<td>n.s.</td>
<td>41.2 ± 8.4</td>
<td>29.3 ± 7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RLS-Qol (p-value)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td>0.008</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI (BL)</td>
<td>10.1 ± 7.3</td>
<td>11.3 ± 8.7</td>
<td>9.3 ± 6.2</td>
<td>n.s.</td>
<td>8.4 ± 7.8</td>
<td>11.1 ± 7.0</td>
<td>0.08</td>
</tr>
<tr>
<td>BDI (FU)</td>
<td>8.5 ± 5.7</td>
<td>9.0 ± 7.4</td>
<td>8.1 ± 4.3</td>
<td>n.s.</td>
<td>7.3 ± 5.6</td>
<td>9.8 ± 5.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>BDI (p-value)</td>
<td>0.001</td>
<td>0.005</td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>ESS (BL)</td>
<td>9.0 ± 5.1</td>
<td>9.2 ± 4.5</td>
<td>8.9 ± 5.5</td>
<td>n.s.</td>
<td>8.4 ± 5.2</td>
<td>9.4 ± 5.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESS (FU)</td>
<td>8.7 ± 4.6</td>
<td>9.2 ± 4.1</td>
<td>8.4 ± 4.8</td>
<td>n.s.</td>
<td>7.8 ± 4.7</td>
<td>9.3 ± 4.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESS (p-value)</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

NP- : Subgroup of patients free of neuropsychiatric comorbidity, NP+ : subgroup of patients with neuropsychiatric comorbidities.
Table 2. Medication at baseline and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Dose/day</td>
</tr>
<tr>
<td>Untreated</td>
<td>40</td>
<td>n.a.</td>
</tr>
<tr>
<td>Levodopa</td>
<td>42</td>
<td>50-1200 mg</td>
</tr>
<tr>
<td>Pramipexol</td>
<td>7</td>
<td>0.18 – 1.4 mg</td>
</tr>
<tr>
<td>Ropinirol</td>
<td>4</td>
<td>2-4 mg</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>1</td>
<td>4 mg</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>4</td>
<td>2-4 mg</td>
</tr>
<tr>
<td>Tilidin</td>
<td>2</td>
<td>100-150 mg</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>6</td>
<td>600-1800 mg</td>
</tr>
<tr>
<td>In accordance with guidelines</td>
<td>64%</td>
<td>71%</td>
</tr>
</tbody>
</table>
Figure 1. Guideline based therapy of idiopathic RLS according to the guidelines of the German Neurological Society.

* Dopamine agonists include pramipexol (up to 0.54 mg/day), ropinirol (up to 4 mg/day) and rotigotine (up to 4 mg/day). For more detailed dosing information please refer to the drug core data sheets. # Augmentation is defined by either earlier onset of symptoms during the day, worsening of RLS symptoms during the day or L-dopa dose exceeding the maximum of 400 mg/day. RR : regular release, SR : sustained release, IR : immediate release.

Figure 2. Comorbidities in percentage of the whole cohort at baseline.

BPH: Benign prostate hyperplasia, EDS: Excessive daytime sleepiness, OSAS: Obstructive sleep apnea syndrome. Thyroid disorders, mainly struma and medically treated hypothyreosis have a very high prevalence in southern Germany, which is only partially explained by low iodine supply. Low serum ferritin was defined as values < 1 SD of mean normal value.

Figure 3. Impact of neuropsychiatric disease on treatment success.

3A: Percentage of patients who improved regarding RLS symptom severity as measured by International RLS study group rating scale (IRLS). 3B: Percentage of patients who improved regarding RLS related quality of life as measured by RLS quality of life questionnaire (RLS-QoL). NP-: subgroup of patients free of neuropsychiatric comorbidity (n=36); NP+: subgroup of patients with neuropsychiatric comorbidity
BASIC THERAPY OF IDIOPATHIC RESTLESS LEGS SYNDROME

RLS with problems to fall asleep
- rL-dopa 100-200 mg
  1 hour prior to bedtime
- Dopamine agonist *
  2 hours prior to bedtime

RLS with problems to stay asleep
- sr+rr L-dopa 100-200 mg
  1 hour prior to bedtime
- ir L-dopa 100 mg

RLS during the day
- Intermittent RLS < 3x/Week
- Dopamine agonist *
  several daily doses
- RLS > 3/Week

TREATMENT OF SPECIFIC PROBLEMS

Contraindications for dopaminergic drugs

Lack of response to dopaminergic drugs

Augmentation *
- under therapy with dopamine agonists
  Dose reduction
  Dose splitting
- under therapy with L-dopa

First choice:
- Opioids (tilidin, tramadol)
Second choice:
- Antiepileptics (gabapentin, pregabalin)

Dopamine agonist *