Sleep Medicine 16 (2015) 1252–1258

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

# Natural course of restless legs syndrome/Willis–Ekbom disease: long-term observation of a large clinical cohort

Thomas Mitterling [a,b], Anna Heidbreder [a], Ambra Stefani [a], Josef Fritz [c], Hanno Ulmer [c], Werner Poewe [a], Birgit Högl [a,*]

[a] Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria
[b] Department of Neurology, Wagner-Jauregg Hospital, Linz, Austria
[c] Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria

ARTICLE INFO

*Article history:*
Received 24 March 2015
Received in revised form 28 May 2015
Accepted 31 May 2015
Available online 20 July 2015

*Keywords:*
Neurology
Augmentation
Pharmacotherapy
Follow-up

ABSTRACT

*Objective:* Although restless legs syndrome (RLS)/Willis–Ekbom disease (WED) is a common neurological disorder, data on the long-term course and management of the disease are scarce. The aim of the current study was to extend the knowledge on the long-term clinical course and treatment outcome of RLS/WED.

*Methods:* In this retrospective analysis, we performed a chart review of consecutive visits of 160 patients with definite RLS/WED from the RLS/WED database of the Innsbruck Medical University.

*Results:* A total of 160 patients (58.8% female, aged 58.9 years, range 21.5–86.8 years) met inclusion criteria of two or more visits during a follow-up of at least five years. The duration of the observational period was 8.1 ± 2.9 years. During the observational period, the percentage of treated patients increased (first vs last visit: 67.5% vs 77.5%). Of the patients, 59.4% had one or more switches of medication. Overall the RLS/WED severity, evaluated using a combined severity score (CSS) ranging from 1 to 5, decreased between the first and last visits (median [range], first visit: 3 [1–5] vs last visit 2.5 [1–5]; $p < 0.001$). Symptoms improved in 55.0% of patients, worsened in 10.6%, and remained unchanged in 34.4% during the observational period. Augmentation of RLS/WED occurred in 42 patients (13/42 as the presenting cause; 29/42 occurring during treatment after 4.1 years). The annual rate of augmentation for subjects on dopaminergic medication was 8.1%.

*Conclusions:* Our data suggest that, with the possibility of regular treatment adjustments, RLS/WED remains treatable in the majority of patients over years. Nevertheless, in this study, despite the overall decreased severity, RLS symptoms remained unchanged or worsened in 45% of the patients during the observational period.



## 1. Introduction

Restless legs syndrome (RLS)/Willis–Ekbom disease (WED) is a common neurological disorder defined by an urge to move the legs, usually accompanied by uncomfortable sensations, which are relieved by movement and show a circadian rhythmicity [1,2]. Up to 10% of the general population is affected, and 1.5%–3% have clinically relevant RLS/WED symptoms [3–5]. The age of onset of symptoms can range from childhood to advanced age, with familial cases tending to start earlier in life [6,7]. RLS/WED symptom severity varies intra- and interindividually, between intermittent RLS/WED symptoms, occurring less than once per week, and a chronic persistent course with symptoms on average more than twice per week [2]. Few studies have focused on the long-term course of the disorder.

Two long-term follow-up studies of the general population, one conducted in Germany using three questions based on the four RLS/WED minimal criteria for diagnosis of RLS/WED, and the other conducted in Japan with diagnosis made in a personal interview, showed a persistence of RLS/WED diagnosis in 50% of subjects in a follow-up period of 2.2 years and 5.2 years or two years apart, indicating a fluctuating course of the disease [8,9]. On the other hand, a more recent study conducted in a cohort of RLS/WED patients showed that in about 60% of patients, no clinically relevant change in RLS/WED severity occurred in a period of three years [10].

Studies with focus on the long-term efficacy of RLS/WED-specific treatment showed that only a proportion of patients derive persistent benefit from dopamine agonist (DA) treatment [11–13].

To extend the knowledge on the long-term clinical course of RLS/WED and treatment outcome, we conducted a retrospective analysis

* Corresponding author. Department of Neurology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. Tel.: +43 512 504 23811; fax: +43 512 504 23842.
*E-mail address:* birgit.ho@i-med.ac.at (B. Högl).

http://dx.doi.org/10.1016/j.sleep.2015.05.028
1389-9457/

of patient charts of RLS/WED patients who were followed up for a minimum of five years at the sleep disorders centre of the Department of Neurology of the Medical University of Innsbruck, Austria.

## 2. Methods

### 2.1. Study subjects

For this retrospective analysis, patients were selected from the RLS/WED database of the sleep disorders clinic of the Department of Neurology at Innsbruck Medical University. In this register, all patients with definite RLS/WED who give consent to be registered are entered. Atypical or doubtful cases are not included. Diagnosis of RLS/WED is made according to standard criteria [1] in an interview by a clinician with long-term expertise in sleep medicine supervised by a board-certified expert in sleep medicine. RLS/WED mimics [14] were carefully excluded.

Only subjects with at least two consecutive visits to the sleep laboratory and a minimum observation time of five years between the first and last visits were selected. Subjects with Parkinson's disease (PD) and multiple system atrophy (MSA) were excluded to avoid the potential confusion of assigning specific therapy to one or the other disease. This study was approved by the local ethics committee, and all patients gave written informed consent.

### 2.2. Data reporting and analysis

Data were extracted from patient charts of consecutive visits to the sleep centre (earliest visits 1994; latest visits 2014). Visits that were conducted during participation in a pharmaceutical trial were not included. For each visit, the following data were extracted: information on RLS/WED severity, presence of augmentation, information on medication, and laboratory investigations.

RLS/WED severity for each visit was reported as the score of the International Restless Legs Syndrome Study Group (IRLSSG) Severity Scale [15] (abbreviated herein as IRLS). If the IRLS was not available, the Clinical Global Impression Scale, Item 1 (CGI-1) [16] was summarized from the patient's literal symptom description reflected in the patient chart (IRLS: $n = 832$; CGI: $n = 1084$). For further analysis of RLS/WED severity, both scales were merged into one score (combined severity score, CSS) which ranged from 1 (no symptoms) to 5 (very severe symptoms) (IRLS 0: CSS = 1; IRLS 1–10: CSS = 2; IRLS 11–20: CSS = 3; IRLS 21–30: CSS = 4; IRLS 31–40: CSS = 5; CGI = 1: CSS = 1; CGI = 2: CSS = 2, CGI = 3–4: CSS = 3; CGI = 5–6: CSS = 4; CGI = 7: CSS = 5). To describe the change in severity between the first and last visits, we calculated the difference between the combined severity score and categorized patients as follows: no change (difference between scores 0), improved (difference between first and last visit >0), and worsened (difference between first and last visit <0).

The presence of RLS/WED augmentation was extracted from patient reports according to standard criteria [17]. No attempt was made to differentiate clinically meaningful augmentation from lesser degrees. The end of one single augmentation episode was defined by resolution of symptoms at the next visit. In addition, we calculated the annual augmentation rate for patients on RLS-specific treatment for at least five years.

Regarding medication, all prescribed substances approved for RLS/WED by medical agencies were captured and extracted. These included levodopa, dopamine agonists, opioids and opioid receptor ligands, α2δ ligands, and anticonvulsants, as well as iron substitution in case of low ferritin values according to international guidelines [18]. For patients receiving opioids (either tramadol or fentanyl) for other indications, these were nonetheless counted as RLS/WED treatment, since effects on RLS/WED could not be excluded. For each medication, we documented whether it was taken continuously or intermittently. In case of a patient taking more than one RLS/WED medication simultaneously, all medications were documented separately. For each visit and each medication, we separately reported whether dose was increased or decreased, whether medication was switched to another substance, and whether medication was started or stopped. In case of any change to the substance, we indicated whether the change was performed by the sleep laboratory, by an outside health care provider, or by the patient's own initiative. All visits were analysed with regard to intermittent changes, ie, medication status at which the patient presented to the sleep laboratory and the medication status after the visit, which reflected the decision made during the visit. For simplification, changes in each single substance were taken together for continuous or intermittent RLS/WED medication, since, because some subjects were on combination therapy, multiple counts were possible at the same time (eg, increase and change in medication). A statistical comparison of medication doses at the first and last visits was not done due to unavailability of specific RLS/WED medication at the first or last visit in the observational period (ie, rotigotine, pregabalin, oxycodone at the first visit; cabergoline, pergolide at the last visit).

Laboratory data were available for 670 visits. The data included in this analysis were haemoglobin, mean corpuscular volume, ferritin, iron, transferrin, transferrin saturation, and C-reactive protein. Because of the influence of inflammation on ferritin, laboratory investigations with C-reactive protein values of >0.5 μg/L were excluded from analysis ($n = 83$).

All extracted data were entered into a database for further analysis.

### 2.3. Statistical analysis

Statistical analysis was done using SPSS for Windows version 20.0 software. Data are given as mean ± standard deviation for quantitative data or frequencies for qualitative data, as applicable. Normal distribution was investigated using the Shapiro–Wilk test. Group comparisons were made using one-way analysis of variance or Kruskal–Wallis test for continuous variables or the $\chi^2$ test for categorical variables. In the case of related variables, the Wilcoxon rank-sum test for paired observations was used. For all tests, a significance level of $\alpha < 0.05$ (two-sided) was used.

## 3. Results

### 3.1. Description of sample

A total of 755 patients in the RLS/WED database of the Innsbruck Medical University were screened; of these, 160 patients met the inclusion criteria of more than two visits in a minimum follow-up period of five years. Due to the digitalization process for patient charts in the centre, some charts of patients with first visit before 2000 might not have been available; therefore, some patients might not have been included, or for other patients the observational period might have been longer. The median age at the first visit was 58.9 years (range 21.5–86.8) years, 94 patients (58.8%) were female, and 66 patients (41.2%) were male. In total 1916 visits were performed and analysed in the 160 patients. On average, patients had 1.5 ± 0.6 (range 0.2–3.7) visits per year. The interval from the first to the last visit was 8.1 ± 2.9 years (range 5.0–19.3 years); 65.5% of patients had a follow-up interval of five to nine years, 20.9% of nine to 13 years, 5.2% of 13 to 17 years, and 1.2% of >17 years.

### 3.2. Comparison of medication after first and last visits

At the first presentation to the sleep centre, 46 patients (28.8%) had RLS/WED-specific therapy (35 monotherapy; 11 combination-therapy [indicating more than one substance simultaneously; two

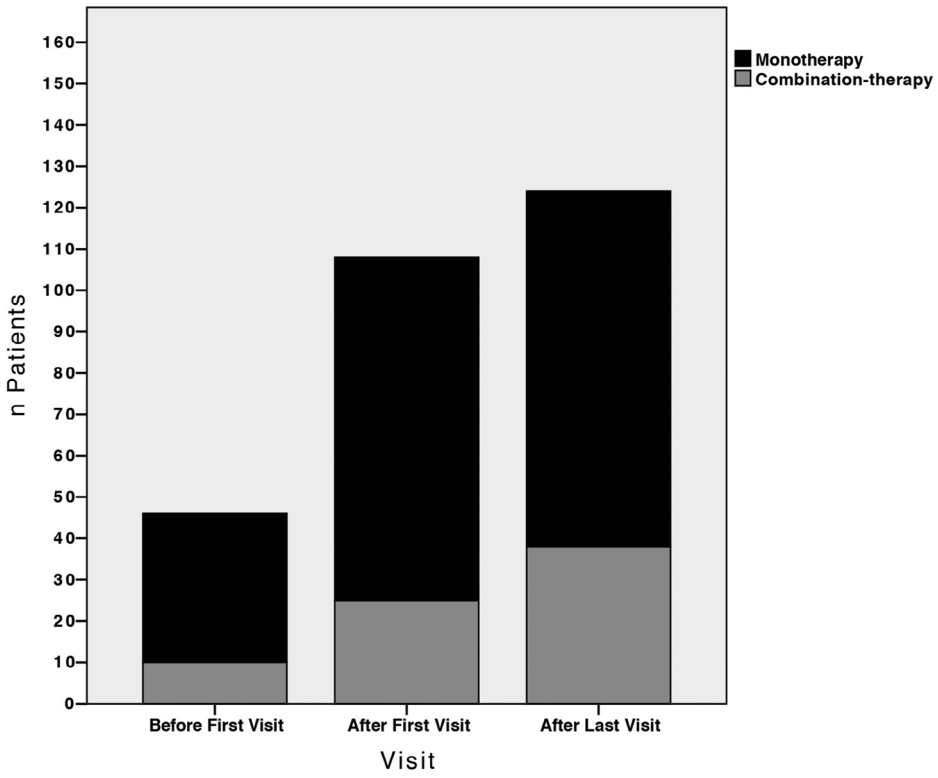


**Fig. 1.** Comparison of monotherapy and combination therapy before the first visit, at the first visit, and at the last visit.

substances: 10 patients; more than two substances: one patient]) (Fig. 1). Levodopa was taken in 25 cases (15.6%), dopamine agonists in 20 cases (12.5%) and valproic acid in one case (0.6%). Patients on combination therapy additionally took levodopa (54.5%, $n = 6/11$), dopamine agonists (18.2%, $n = 2/11$), iron substitution (27.3%, $n = 3/11$), or opioids (9.9%, $n = 1/11$).

After their first consultation in the sleep clinic 108 subjects (67.5%) received RLS/WED-specific therapy, including iron in the case of low ferritin values. Of these subjects, 83 (76.9%) were on monotherapy, and 25 (23.1%) were on combination therapy (two substances: 23 patients; more than two substances: two patients) (Fig. 1). Medication was prescribed as daily medication in 90.1% and as intermittent medication in 11.1% (either as monotherapy or as additional intermittent medication). A detailed overview of substances prescribed during the first visit is presented in Table 1 (upper panel).

**Table 1**
Medication at first and last visits.

| | First medication *n* (%)[a] | Daily/intermittent *n* (%) |
|---|---|---|
| First visit | | |
| Levodopa | 46 (42.6%) | 37 (34.3%)/9 (8.3%) |
| Dopamine agonists | 54 (50%) | 52 (48.2%)/2 (1.9%) |
| Opioids | 2 (1.9%) | 0 (0.0%)/2(1.9%) |
| α2δ ligand | 0 (0%) | 0 (0.0%)/0 (0.0%) |
| Anticonvulsants | 2 (1.9%) | 2 (1.9%)/0(0.0%) |
| Iron | 7 (6.5%) | 7 (6.5%)/0(0.0%) |
| Last visit | | |
| Levodopa | 17 (13.7%) | 5 (4.0%)/12 (9.7%) |
| Dopamine agonists | 88 (80.0%) | 83 (66.9%)/5 (4.0%) |
| Opioids | 15 (12.1%) | 14 (11.3%)/1 (0.8%) |
| α2δ ligand | 9 (7.3%) | 9 (7.3%)/0 (0%) |
| Anticonvulsants | 0 (0%) | 0 (0%)/0 (0%) |
| Iron | 1 (0.8%) | 1 (0.8%)/0 (0%) |

[a] Sums up to more than 100% since intermittent and daily medication is reported combined.

In the case of patients needing a second medication, 18.6% ($n = 20$) of the 108 treated patients were prescribed levodopa or iron (9.3% respectively). In addition, iron was prescribed as a third medication in 1.9% of patients ($n = 2/108$). The median doses at the first visit for dopamine agonists were as follows: 0.18 mg (0.088–0.7 mg) for pramipexole ($n = 35$); 1.5 mg (0.25–2 mg) for ropinirole ($n = 5$); 0.25 mg (0.125–0.25 mg) for pergolid ($n = 5$); 2.0 mg (2.0–2.0 mg) for cabergoline ($n = 4$); and 1.0 mg (1.0–3.0 mg) rotigotine ($n = 3$). For levodopa ($n = 37$), the median dose was 100 mg (50–150 mg), and for levodopa continuous release ($n = 11$) it was 100 mg (50–100 mg). Substances taken by fewer than three patients were considered negligible.

After the last visit to the sleep centre (conducted between 2006 and 2014), 124 patients (77.5%) had RLS/WED-specific therapy, including iron in the case of low ferritin values; 86 of these patients (69.4%) were on monotherapy, and 38 were on on combination therapy (two substances: 36 patients; more than two substances: two patients) (Fig. 1). This medication was prescribed as daily medication in 89.5% of patients and as intermittent medication in 13.7% (either as monotherapy or as additional intermittent medication). A detailed overview on the substances used at the last visit is shown in Table 1 (lower panel). In the case of patients needing more than one medication, they were prescribed α2δ ligands (9.7%, $n = 12/124$), iron (8.1%, $n = 10/124$), and opioids (5.7%, $n = 7/124$). In the case of a third continuous medication, iron was used (1.6%, $n = 2/124$). The median dose at the last visit for dopamine agonists was 0.27 mg (0.088–1.4 mg) for pramipexole ($n = 65$), 2.0 mg (1.0–4.0 mg) for rotigotine ($n = 13$), and 2.0 mg (2.0–4.0 mg) for ropinirole continuous release ($n = 4$). Patients taking opioids had a median of 20 mg (10–70 mg) oxycodon continuous release ($n = 14$) or fentanyl transdermal patch ($n = 3$) 50 μg (12.0–75.0 μg). Patients with α2δ ligands had either pregabalin ($n = 10$) 300 mg (150–450 mg) or gabapentin ($n = 11$) 600 mg (300–1800 mg). Levodopa ($n = 17$) was taken at a median dose of 100 mg (100–150 mg). Substances taken by fewer than three patients were considered negligible.

**Table 2**
Medication use during observational period.

| | First medication[a] % of visits | Second medication % of visits | Third medication % of visits |
|---|---|---|---|
| Levodopa | 20.4 | 4.2 | 0.6 |
| DA | 70.9 | 1.4 | 0.0 |
| Opioids | 8.5 | 4.4 | 0.1 |
| α2δ ligand | 4.7 | 6.0 | 0.3 |
| Iron | 2.1 | 9.4 | 0.9 |

Medication use during observational period summarized for medication classes.
DA, dopamine agonists.
[a] Sums to more than 100%, as intermittent and daily medication are reported combined.

**Table 3**
Medication switches during observational period.

| Medication switch[a] | % |
|---|---|
| DA → DA | 43.7% |
| LD → DA | 26.5% |
| DA → opioid | 7.9% |
| DA → α2δ ligands | 5.7% |

Medication switches during observational period summarized for medication classes.
DA, dopamine agonist; LD, levodopa.
[a] Other switches were omitted because of low frequency.

### 3.3. Ferritin levels at the first and last visits

At the first visit, laboratory workup of 64 patients included ferritin level. The median was 43.5 μg/L (range 4.0–405.0 μg/L); 53% of patients (34/64) had a ferritin level <50 μg/L. At the last visit, a ferritin level was available for 46 patients (median 84.0 μg/L, range 7.0–386.0 μg/L); 28% of patients (13/46) had a ferritin level <50 μg/L.

### 3.4. Medication changes during the observational period

Of 1916 visits, patients were receiving RLS/WED therapy for a median of 96.1% of their visits (range 0–100%), implying that 50% of patients had RLS/WED-specific therapy at 96.1% or more of their visits. In 56.4% of visits, patients were on monotherapy, in 25.5% on combination therapy (two substances: 22.6%; more than two substances: 2.8%), and in 18.1% no therapy. In 92.2% of visits with patients receiving therapy, patients were on continuous medication, whereas intermittent therapy was recorded in 13.3% of visits, either as monotherapy or as intermittent adjunct to continuous medication. Table 2 provides an overview on the drugs used during the observational period.

The medication remained unchanged in a median of 55.3% of visits (0–91%). A switch to another substance was done in a median of 11.0% of visits (range 0–60%), and 95 patients (59.4%) had at least one switch of medication. An overview of medication switches during the observational period is given in Table 3. A new additional medication was started in a median of 17.8% of visits (0–100%), an increase of substance dose was prescribed in a median of 0% of visits (0.0–40%), and a decrease was prescribed in a median of 0% of visits (0–25.0%). Reasons for these adjustments were insufficient treatment (46%), a medical indication (34.3%), or augmentation (11.7%).

### 3.5. Evolution of RLS/WED severity

An overview of symptom severity according to the CSS at the first and last visits is given in Fig. 2. Although at the first visit 132 patients presented with moderate to very severe RLS/WED symptoms, at the last visit, 80 patients presented within the range of moderate to very severe symptoms. Comparison of the combined symptom severity score showed significant differences between the visits (first visit 3, range 1–5, vs last visit 2.5, range 1–5; $p < 0.001$).

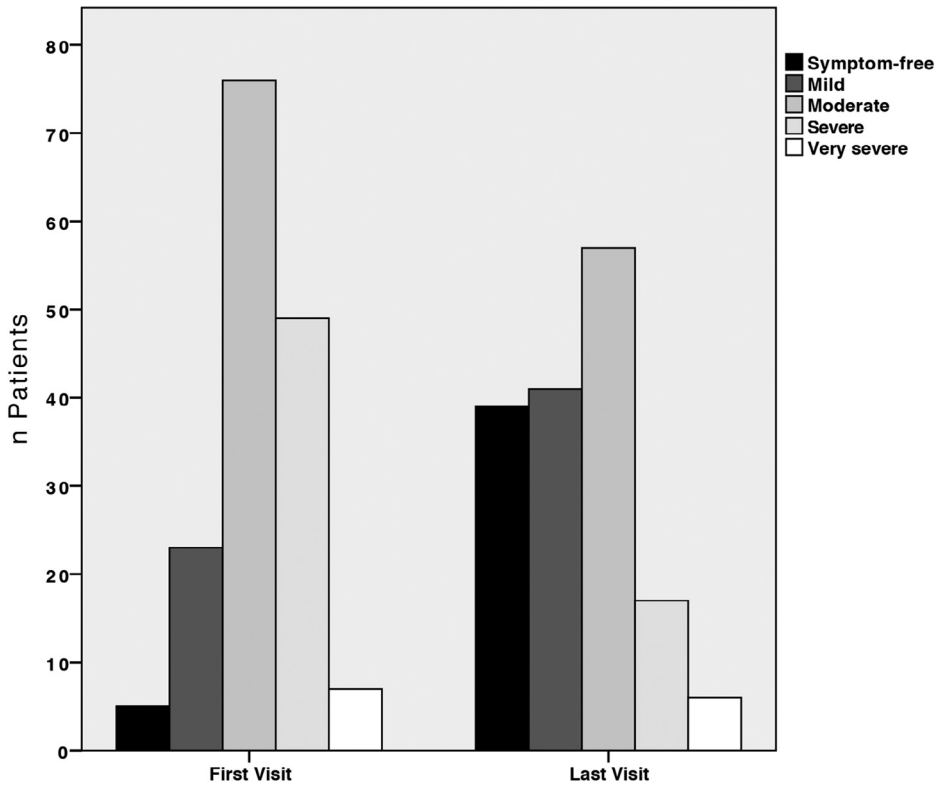


**Fig. 2.** Combined severity score for the first and last visits for the whole sample ($n = 160$).

**Table 4**
Medication at first augmentation.

| Medication at first augmentation | First daily medication[a] | Second daily medication[a] | Third daily medication[a] |
|---|---|---|---|
| Levodopa | 17 (40.5%) | 6 (14.3%) | 0 (0.0%) |
| DA | 28 (66.7%) | 2 (4.8%) | 0 (0.0%) |
| Opioids | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| α2δ ligand | 0 (0.0%) | 1 (2.4%) | 0 (0.0%) |
| Anticonvulsants | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Iron | 0 (0.0%) | 2 (4.8%) | 0 (0.0%) |
| Outcome medication | | | |
| Levodopa | 8 (19.1%) | 4 (9.5%) | 0 (0.0%) |
| DA | 34 (81.0%) | 0 (0.0%) | 0 (0.0%) |
| Opioids | 6 (14.3%) | 0 (0.0%) | 0 (0.0%) |
| α2δ ligand | 2 (4.8%) | 1 (2.4%) | 0 (0.0%) |
| Anticonvulsants | 0 (0.0%) | 0 (0%) | 0 (0.0%) |
| Iron | 0 (0.0%) | 7 (16.7%) | 2 (4.8%) |

DA, dopamine agonists.
[a] Note that count might sum to more than 100% because multiple counts are possible.

Analysis of the change in severity from the first to the last visit showed that in 55% of patients, RLS/WED symptoms improved, in 10.6% symptom severity worsened, and in 34.4% symptoms remained unchanged. The same decrease in severity was found when analysing only those patients who were not treated at the first visit (first visit 3, range 1–5, vs last visit 2.5, range 1–5; $p < 0.001$ ). The combined severity score for these patients improved in 54.4% of patients, worsened in 13.2%, and remained unchanged in 32.5% in the observational period.

### 3.6. Augmentation

#### 3.6.1. First augmentation

In 42 patients (26.3%; 28 female and 14 male), case notes provided clear evidence for RLS/WED symptom augmentation. A total of 13 patients presented with augmentation at the first visit, and 29 patients presented with augmentation during treatment at a mean interval of 4.1 years (range 0.5–14.1 years) from the first visit. According to the combined severity score, three patients had mild RLS/WED symptoms, nine moderate, 19 severe, and 11 very severe symptoms. In 28 patients (66.7%), augmentation occurred on monotherapy and in 14 (33.3%) on combination therapy (all on two substances). A detailed overview on the substances under which augmentation occurred is given in Table 4. For treatment of augmentation, a change of substance was made in 26 cases (61.9%), an increase in medication dose in five cases (11.9%), the start of a new additional medication in eight cases (19.0%), and cessation of medication in four cases (9.5%). In 12 cases (28.6%), no changes in medication were done; these patients were either switched to another medication at a later visit or no changes in medication were made in agreement with the patient (Table 4). In case of a switch to another substance, this was mostly from one dopamine agonist to another dopamine agonist (53.8%, $n = 14/26$) followed by switches from levodopa to a dopamine agonist (34.6%, $n = 9/26$) (Table 5).

#### 3.6.2. All augmentations

A total of 42 patients (26.3%) presenting with or developing augmentation had a total of 90 episodes of augmentation, 52.4% ($n = 22/42$) of these patients augmented more than once (range 1–5 times). In 38.9% ($n = 35$) of cases, augmentation occurred on combination therapy (two substances: 33.3%; more than two substances: 5.6%). At the time of augmentation, most patients were on dopamine agonists (81.1%) and levodopa (23.3%). In one case, augmentation occurred on methadone taken as daily monotherapy. Patients on combination therapy beyond dopamine agonists additionally had levodopa (31.4%), α2δ ligands (22.9%) (gabapentin), opioids (22.9%) (tramadol), or dopamine agonists (5.7%) as simultaneous therapy. The annual augmentation rate for patients on dopaminergic therapy for at least five years ($n = 81$) was 8.1%; the annual augmentation rate for all RLS-specific drugs was 8.4%. The presence of augmentation led to a switch of medication in 58.9% of cases. These switches were most often from a dopamine agonist to another dopamine agonist (56.6%; $n = 30/53$), followed by switches from levodopa to a dopamine agonist (22.6%; $n = 12/53$) (Table 6) In 40.0% of augmentations, medication was not changed, in 11.1% the medication dose was increased, in 14.4% a new additional medication was started, and in 6.7% the medication was stopped.

**Table 5**
Medication switches at first augmentation.

| Medication class | % (n) | Substance[a] | % (n) |
|---|---|---|---|
| DA → DA | 53.9% (14/26) | PPX → CBG | 42.9% (6/14) |
| | | PPX → ROT | 28.6% (4/14) |
| LD → DA | 34.6% (9/26) | LD → PPX | 44.4% (4/9) |
| | | LD → RPR | 22.2% (2/9) |
| DA → α2δ ligand | 7.7% (2/26) | PPX → GBP | 50.0% (1/2) |
| | | PPXCR → GBP | 50.0% (1/2) |
| DA → opioid | 3.8% (1/26) | PPX → OXY | 100.0% (1/1) |

Medication switches are shown for medication class and substance.
CBG, cabergoline; DA, dopamine agonist; GBP, gabapentin; LD, levodopa; MET, methadone; OXY, oxycodone; PPX, pramipexole; PPXCR, pramipexole continuous release; ROT, rotigotine; RPR, ropinirole.
[a] Other switches were omitted because of low frequency.

#### 3.6.3. Comparison of never-augmented patients with at least-once augmented patients

In the whole sample, 118 patients never experienced augmentation (NAUG), whereas 42 patients augmented at least once (AUG). AUG patients were significantly older than NAUG patients at the first visit to the sleep laboratory (NAUG vs AUG: 57.7 21.5–78.0 vs 63.3 34.7–86.8; $p = 0.013$). RLS/WED symptom severity according to the CSS at this point was lower for NAUG patients compared to AUG subjects (NAUG vs AUG: 3 1–5 vs 4 3–5; $p = 0.001$). After excluding patients who were augmented already at the first visit, there remained a trend towards higher severity in the AUG group (NAUG vs AUG: 3.0 1–5 vs 3.0 3–5; $p = 0.055$). Regarding medication, 61.0% of NAUG patients had RLS/WED-specific therapy, whereas 83.3% of AUG subjects had therapy at the first visit to the sleep laboratory. Ferritin levels did not differ between these two groups (NAUG vs AUG: 58.0 4.0–405.0 μg/L vs 33.0 4.0–190.0 μg/L; $p = 0.172$).

At the last visit to the sleep laboratory, no differences in symptom severity were found between the groups (NAUG vs AUG: 2 1–5 vs 3 1–5; $p = 0.069$). Whereas 71.2% of NAUG patients had RLS/WED-specific therapy, 95.2% of AUG patients were on RLS/WED therapy

**Table 6**
Medication switches for all augmentations.

| Medication class | % (n) | Substance[a] | % (n) |
|---|---|---|---|
| DA → DA | 56.6% (30/53) | PPX → CBG | 36.7% (11/30) |
| | | PPX → ROT | 26.7% (8/30) |
| LD → DA | 22.6% (12/53) | LD → PPX | 50.0% (6/12) |
| | | LD → ROT | 16.7% (2/12) |
| | | LD → RPR | 16.7% (2/12) |
| DA → Opioid | 15.1% (8/53) | PPX → OXY | 37.5% (3/8) |
| | | ROT → MET | 25.0% (2/8) |
| DA → α2δ ligand | 5.7% (3/53) | CBG → GBP | 33.3% (1/3) |
| | | PPX → GBP | 33.3% (1/3) |
| | | PPXCR → GBP | 33.3% (1/3) |

Medication switches are shown for medication class and substance.
CBG, cabergoline; DA, dopamine agonist; GBP, gabapentin; LD, levodopa; MET, methadone; OXY, oxycodone; PPX, pramipexole; PPXCR, pramipexole continuous release; ROT, rotigotine; RPR, ropinirole.
[a] Other switches were omitted because of low frequency.

at the end of the observational period. The use of non-dopaminergic medication was more common in AUG patients (NAUG 12.7% vs AUG: 64.2%). No significant differences were found for ferritin levels at the last visit (NAUG vs AUG: 86.0 12.0–386.0 μg/L vs 62.0 7.0–284.0 μg/L; $p = 0.348$).

## 4. Discussion

This study provides long term follow-up data on the natural course of RLS/WED in a large cohort of patients who received standard medical therapy and were followed over a minimum of five years. It is the first study focussing not only on RLS/WED severity over time but also on long-term management and treatment outcomes. Compared to RLS/WED symptom severity at the first presentation to the sleep laboratory, symptom severity was lower at the end of the observational period in the whole cohort as well as in patients who were not treated at the first visit. Our data suggest that in a clinical cohort of RLS/WED patients with the possibility of frequent treatment adjustments, RLS/WED remains manageable over a period of five years in the majority of patients; however, in a considerable proportion of subjects, severity may increase or may not change.

### 4.1. RLS/WED patients and treatment

Although at the first visit to the sleep laboratory only 28.8% of patients were pre-treated for RLS/WED, after consultation 67.5% had a specific medication. This number increased up to 77.5% until the last visit. It has been noted that among all patients who have RLS/WED, only a fraction of patients need treatment, mainly those who experience frequent symptoms [19]. In the general population, the treatment wish of patients with a known and unknown diagnosis of RLS/WED was reported at around 20% [20]. Our patient collective, however, consisted of patients who attended the sleep disorders clinic for RLS/WED and is therefore likely to reflect patients with frequent symptoms. Although the number of treated patients was high at the last visit, still more than 20% patients were without treatment, showing that there is a subpopulation of RLS/WED patients who either do not require or do not wish specific treatment. This adds to the broad spectrum of RLS/WED, ranging from ancillary diagnosis to augmentation [21].

In line with current treatment guidelines for RLS/WED [13], the most commonly used substances in our cohort were dopamine agonists. Although at the first visit the distribution of substances had a clear predominance of dopaminergic treatment, at the last visit an increase in non-dopaminergic medication was noted. This further corroborates the well-known issue of limited usefulness of dopaminergic treatment in RLS/WED, and shows that in the case of ineffectiveness of dopaminergic therapy, non-dopaminergic treatment reflects a valuable alternative [22,23] but also likely reflects the availability of new substances useful in treating RLS/WED. In addition, medication dose at the last visit seemed to be higher than at the first visit, which might best be explained by either natural disease progression or loss of efficacy of medication.

The fact that the median of patients were taking RLS/WED-specific therapy on 96.1% of visits might show that RLS/WED patients in a sleep disorders clinic have a need for treatment. However, looking at the number of changes in specific medication, 60% of patients in the cohort had at least one switch in continuous medication; thus, it becomes apparent that adjustments in medication are frequently necessary. The adjustments ranged from a switch to another substance to a start of a new additional treatment or an increase in dose. On one hand, this might reflect the limited clinical utility of dopaminergic medication, which was most often initial therapy in our cohort; on the other hand, this could reflect a fluctuating course of RLS/WED symptoms.

### 4.2. Course of RLS/WED severity over time

In our patient group, RLS/WED severity decreased from the first to the last visit. Since the number of treated patients increased from 28.8% to 77.5% during the observational period, this decrease in overall symptom severity could be attributed to specific treatment. It also shows that RLS/WED treatment is effective for a period of at least five years in the majority of patients, albeit with the need for adjustments as stated above. This result is in contrast to findings from a study in an RLS/WED population, which showed no relevant changes in RLS/WED severity over a 3-year period [10]. This difference might best be explained by the fact that at our first visit, only 30% of patients were on RLS/WED-specific medication, whereas in the study by Fuhs et al., 93% were on RLS/WED-specific medication at the baseline visit [10]. Nevertheless, although 55% of our patients still had improvement in RLS/WED symptoms (as measured by CSS) between their first and last visits, our data also show that almost half of the patients (45%) had no improvement or had even worse symptoms than initially after the end of the observational period.

### 4.3. Augmentation

The total rate of augmentation of 26.3% in this clinical cohort is well in line with the existing literature on the rate of augmentation on dopaminergic medication [24–28]. In all cases except one, augmentation occurred under the influence of dopaminergic medication. This further adds to the pathophysiological concept of a hyperdopaminergic state causing this side effect [29]. The annual rate of augmentation for patients who were on dopaminergic medication for at least five years was 8.1% and appears rather low in comparison to rates in the literature [30]. The most probable explanation for this might be the practice, in our sleep laboratory, of keeping the patient on a low dose of dopaminergic medication.

In one case, augmentation occurred on methadone monotherapy. This patient was an 89-year-old woman who fulfilled diagnostic criteria of augmentation on a methadone daily dose of 5 mg. An increase in methadone dose was not made, as the patient had severe central apnea syndrome during polysomnography. The patient was switched to gabapentin, and symptoms of augmentation resolved. Some augmented patients were on simultaneous treatment with non-dopaminergic substances, either tramadol or gabapentin. We cannot differentiate whether this simultaneous treatment with α2δ ligands or opioids was a co-factor leading to augmentation, but it seems very likely that these medications were initiated due to subthreshold/beginning augmentation or loss of efficacy. Although the presence of augmentation on tramadol treatment has been described [31] in a large observational study, no signs of augmentation occurred on methadone treatment [11]. In addition, in a recent study, only a few patients were classified as experiencing augmentation while on α2δ ligand treatment [23].

Because of augmentation, a switch of medication was necessary in 60% of cases. These changes most often comprised switches from short-lasting substances to long-lasting ones, either dopaminergic or non-dopaminergic. This practice reflects current recommendations for treating dopaminergic augmentation [32].

In comparison to never-augmented patients, those patients who augmented at least once had a trend towards more severe RLS/WED symptoms at the first visit to the sleep laboratory but not at the last visit. In addition, patients who augmented at least once were older than never-augmented patients and were already on treatment more frequently at the first visit. These results reflect factors associated with the development of augmentation reported in the literature [28].

### 4.4. Study strengths and limitations

The major strength of the current work is the long observational period of more than five years in a clinical RLS/WED cohort of 160 patients. Moreover this study was not limited to one specific RLS/WED medication, and was designed to analyse every change in RLS/WED-specific medication during consecutive visits. Another strength is that this study was conducted in a sleep disorders clinic with special expertise in RLS/WED. One potential limitation is the retrospective design of the current study.

In conclusion, this study presents data from a large RLS/WED cohort followed up over an average (±SD) of 8.1 ± 2.9 years. Our data suggest that, with the current possibilities of dopaminergic and non-dopaminergic therapy and adjustments according to clinical need, RLS/WED remains manageable over the years in the majority of patients, but that in almost half of these patients (45% in this study) symptoms may be unchanged or may worsen.

## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.05.028.

## Acknowledgements

This study was supported by a grant from the Translational Research Fund of the government of Tyrol Austria to Birgit Högl. We would like to express our gratitude to Prof. Richard Allen for the fruitful discussion of the data and advice in preparing the manuscript.

## References

[1] Allen RP, Picchietti D, Hening WA, et al. Restless Legs Syndrome Diagnosis and Epidemiology Workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. 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.
[2] Allen RP, Picchietti DL, Garcia-Borreguero D, 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.
[3] Högl B, Kiechl S, Willeit J, et al. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. Neurology 2005;64:1920–4.
[4] Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–92.
[5] Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Mov Disord 2011;26:114–20.
[6] Winkelmann J, Muller-Myhsok B, Wittchen HU, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol 2002;52:297–302.
[7] Whittom S, Dauvilliers Y, Pennestri MH, et al. Age at onset in restless legs syndrome: a clinical and polysomnographic study. Sleep Med 2007;54–9.
[8] Kagimura T, Nomura T, Kusumi M, et al. Prospective survey on the natural course of restless legs syndrome over two years in a closed cohort. Sleep Med 2011;12:821–6.
[9] Szentkiralyi A, Fendrich K, Hoffmann W, et al. Incidence of restless legs syndrome in two population-based cohort studies in Germany. Sleep Med 2011;12:815–20.
[10] Fuhs A, Bentama D, Antkowiak R, et al. Effects of short- and long-term variations in RLS severity on perceived health status – the COR Study. PLoS ONE 2014;9(4):e94821. doi:10.1371/journal.pone.0094821.
[11] Silver N, Allen RP, Senerth J, et al. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011;12:440–4.
[12] Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med 2012;13:1280–5.
[13] Garcia-Borreguero D, Kohnen R, Silber MH, 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.
[14] Hening WA, Allen RP, Washburn M, et al. The four diagnostic criteria for restless legs syndrome are unable to exclude confounding conditions ("mimics"). Sleep Med 2009;976–81.
[15] Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[16] National Institute of Mental Health. Early clinical drug evaluation unit (ECDEU). Clinical global impressions. In: Guy W, editor. ECDEU assessment manual for psychopharmacology. Rev ed. Rockville, MD: National Institute of Mental Health; 1976.
[17] García-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine–International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. Sleep Med 2007;8:520–30.
[18] Hening WA. Current guidelines and standards of practice for restless legs syndrome. Am J Med 2007;120(Suppl. 1):S22–7.
[19] Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS Epidemiology, Symptoms, and Treatment) primary care study. Sleep Med 2004;5:237–46.
[20] Happe S, Vennemann M, Evers S, et al. Treatment wish of individuals with known and unknown restless legs syndrome in the community. J Neurol 2008;255:1365–71.
[21] Frauscher B, Gschliesser V, Brandauer E, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med 2009;10:611–15.
[22] Trenkwalder C, Benes H, Grote L, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol 2013;12:1141–50.
[23] Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with parmipexole for restless legs syndrome. N Engl J Med 2014;370:621–31.
[24] Silber M, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep 2003;26:819–21.
[25] Ondo W, Romanyshyn J, Vuonog KD, et al. Long-term treatment of restless legs syndrome with dopamine agonists. Arch Neurol 2004;61:1193–7.
[26] Montplaisir J, Fantini ML, Desaultes A, et al. Long-term treatment with pramipexole in restless legs syndrome. Eur J Neurol 2006;13:1306–11.
[27] Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome. Sleep Med 2004;5:9–14.
[28] Allen RP, Ondo W, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med 2011;12:431–9.
[29] Paulus W, Trenkwalder C. Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome. Lancet Neurol 2006;5:878–86.
[30] Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 2010;9:807–15.
[31] Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. Sleep Med 2006;7:592–3.
[32] García-Borreguero D, Allen RP, Benes H, et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. Mov Disord 2007;22(Suppl. 18):S476–84.