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Cabergoline Compared to Levodopa in the Treatment of Patients with Severe Restless Legs Syndrome: Results from a Multi-Center, Randomized, Active Controlled Trial

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Abstract: We report the first large-scale double-blind, randomly assigned study to compare two active dopaminergic therapies for Restless Legs Syndrome (RLS), the dopamine agonist cabergoline (CAB) and levodopa/benserazide (levodopa). Methods: Patients with idiopathic RLS were treated with fixed daily doses of 2 or 3 mg CAB or 200 or 300 mg levodopa for 30 weeks. Efficacy was assessed by changes in the IRLS (International RLS Severity Scale) and by time to discontinuation of treatment due to loss of efficacy or augmentation. 361 of 418 screened patients (age 58 ± 12 years, 71% females) were randomly assigned and treated (CAB: n = 178; levodopa: n = 183) in 51 centers of four European countries. Baseline IRLS total score was 25.7 ± 6.8. The baseline-adjusted mean change from baseline to week 6 in IRLS sum score was d = −16.1 in the CAB group and d = −9.5 in the levodopa group (d = −6.6, $P < 0.0001$). More patients in the levodopa group (24.0%) than in the CAB group (11.9%, $P = 0.0029$, log-rank test) discontinued because of loss of efficacy (14.2% vs. 7.9%, $P = 0.0290$) or augmentation (9.8% vs. 4.0%, $P = 0.0412$). Adverse events (AEs) occurred in 83.1% of the CAB group and in 77.6% of the levodopa group. In both groups, most frequent AEs were gastrointestinal symptoms (CAB: 55.6%, levodopa: 30.6%, $P < 0.0001$). This first large-scale active controlled study in RLS showed superior efficacy of cabergoline versus levodopa after a 30-week long-term therapy. Tolerability was found more favorable with levodopa than with cabergoline. © 2007 Movement Disorder Society

Key words: restless legs syndrome; therapy; cabergoline; levodopa; augmentation.

The concept, that dopamine agonists (DAs) being the future first line treatment in restless legs syndrome (RLS)[1-4] instead of levodopa was primarily derived from the positive results of recent large multi-center trials which compared to dopamine agonists to placebo.[5-7] However, no large-scale comparative studies between two or more dopaminergic drugs are currently available. Our objective was to directly and prospectively compare the efficacy and tolerability of L-dopa plus decarboxylase inhibitor benserazide with the dopamine agonist cabergoline. We wanted to demonstrate a. non-inferiority in symptom relief of long-acting cabergoline compared to short-acting L-dopa/benserazide after 6 to 8 weeks of short-term treatment and b. superiority of cabergoline

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CALDIR = CAbergoline versus L-Dopa In RLS

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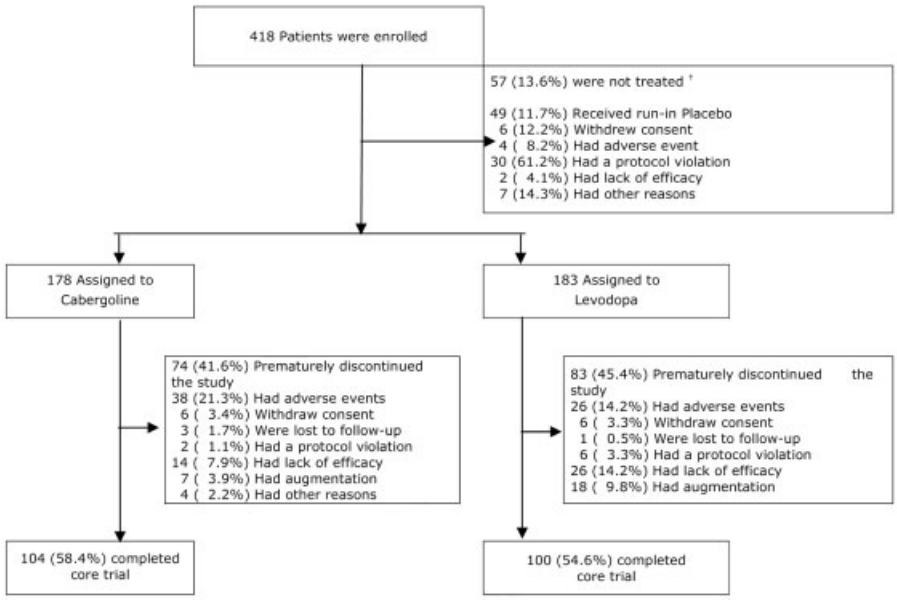

FIG. 1. Patient disposition. Several reasons for exclusion of a patient from the trial could be present.

over L-dopa after 30 weeks of long-term therapy with respect to discontinuation from treatment because of loss of efficacy or augmentation.

L-dopa until recently was the only approved drug for treatment of RLS in some European countries, therefore it was chosen as the "gold standard" for comparison with the dopamine agonist cabergoline. To evaluate different risk-benefit profiles of the two active treatments, frequency of augmentation and loss of efficacy was chosen as a second outcome measure. Augmentation is defined as a paradoxical worsening of RLS during daytime when dopaminergic treatment has been started at night, and is usually characterized by the occurrence of RLS symptoms earlier in the day, with a shorter latency at rest, increase in intensity of symptoms, and spreading of RLS symptoms to previously unaffected areas of the body.[8] Augmentation occurs mostly in RLS patients under chronic treatment with L-dopa[9,10] and is the most troublesome treatment complication of dopaminergic therapy in RLS patients.

PATIENTS AND METHODS

Design

This was a multi-center, international, double-blind, randomized, active-controlled, parallel-group study in the treatment of patients with moderate to severe idiopathic RLS for 30 weeks. Patients had to pass a placebo run-in phase of 1 week prior to baseline. At baseline, they were sequentially assigned to one of the two treatments by the investigators using medication numbers in ascending order for each block of 4 which was allocated to the study site after central randomization. Dose of treatment was further increased in patients with insufficient response but good tolerability at the end of Week 6. The total treatment period lasted till 30 weeks. (Fig. 1)

Study Treatment

Upon randomization all patients were up-titrated to 2 mg cabergoline or 200 mg L-dopa and treated with dose level 1 for 6 weeks (Period 1). The daily cabergoline dose was up-titrated after baseline assessment in 0.5 mg increments to 2.0 mg until day 14 whereas L-dopa was increased in steps of 50 mg, 100 mg, and 200 mg until day 8. In patients who experienced insufficient efficacy without impairing adverse events according to the CGI "therapeutic effect" and the CGI "side effect" items at week 6, dose was increased to daily doses of 3 mg cabergoline or 300 mg L-dopa/75 mg benserazide. No further dose adjustments were permitted during the study. The cabergoline dose was given 3 hours before bedtime, L-dopa was applied in two doses; the first one (50 or 100 mg) was taken 3 hours before bedtime, the second dose (150 or 200 mg) was administered at bedtime. Placebo tablets (cabergoline) and capsules (L-dopa) of identical appearance to active treatments were used to keep the treatment blinded (double-dummy technique with intake of both capsules and tablets by each patient). Patients showing unacceptable gastrointestinal side effects after dose increase at any period of the study could be prescribed the peripheral dopamine-D2 receptor

blocker domperidone in dosages up to 20 mg three times a day.

Diagnosis and Main Criteria for Inclusion

Male and female patients aged 18 to 75 years could participate in the study if they presented with all four clinical manifestations of RLS according to the IRLSSG criteria[8]: Patients had to complain about an urge to move that could be accompanied by uncomfortable or unpleasant sensations in the legs; symptoms begin or worsen during rest, are relieved by movement, and are worse in the evening or at night than during the day. Severity of symptoms had to be at least moderate according to the IRLS total score (IRLS score 10 or higher).[11] In addition a "severity at night" score of ≥4 in the 11-point RLS-6 rating scale (ranging from 0 = "not present" to 10 = "very severe") had to be present.[12] Patients were either de novo or unsatisfied with previous RLS therapy.

Patients with secondary RLS, iron deficiency, or other clinically relevant concomitant diseases were excluded. Patients with established or suspected hypersensitivity to ergot alkaloids or with non-response or intolerability to previous cabergoline or L-dopa therapy, if any, were also excluded. Concomitant use of drugs with a probable influence on RLS was not permitted. Pretreatment with cabergoline or L-dopa (>200 mg/day) had to be discontinued two months prior to screening, and all drugs with an influence on RLS or sleep had to be discontinued at the start of the washout period 1 week before baseline.

Efficacy Evaluations

Assessments to determine efficacy outcome were performed on a regular basis during patients' visits at study sites. The following measures were used: the IRLS (severity rating scale[11] of the International RLS Study Group (IRLSSG) in its version for clinical trials,[13] the RLS-6 severity scales,[12] sleep quality subscale of the Sleep Questionnaire Form A (SF-A),[14] the Quality of Life for RLS questionnaire (RLS-QoL[15]); the Augmentation Severity Ratings Scale (ASRS, 4-item version[16]), and the Clinical Global Impressions (CGI,[17]). Augmentation was defined according to the criteria described above.[8] Loss of efficacy comprises any other dissatisfaction of the patients with the treatment's efficacy. Both events were diagnosed clinically by the investigators at each study site based on interviews with the patients. Investigators were thoroughly trained in the identification of both events by the first author during the investigators' meeting.

Safety Evaluations

Safety was assessed with regard to type and frequency of adverse events, clinically relevant changes in laboratory data and abnormalities observed in the electrocardiography (ECG). In addition, premature discontinuation of the study participation because of tolerability and safety problems was considered as an important safety information. The Epworth Sleepiness Scale (ESS[18]) was applied to assess the amount of excessive daytime sleepiness.

Statistical Methods

Randomly assigned patients who presented at least one assessment of the primary endpoint under medication were included into the intent-to-treat population (ITT). Patients were per-protocol (PP) if they were at least 21 days under treatment with study medication and did not present with a major protocol violation. We used the last-observation-carried-forward method (LOCF) to impute values if no follow-up information was available at the study end.

Short-Term Treatment Period I.

Non-inferior clinical efficacy of cabergoline vs. L-dopa was assessed by use of changes in the IRLS total score between baseline and Week 6 or Week 8 (in the event of dose increase) for the PP population. The non-inferiority margin was calculated as 3 points from the 90% confidence interval of the error of measurement of the IRLS using a mean IRLS score of 21.9 points, a standard deviation of 8.8 points and the reliability coefficient of rit = 0.93 as reported in the IRLS validation study.[11] Both treatments were compared with the least square (LS)-means from an Analysis of Covariance (ANCOVA) model with treatment as a fixed factor and baseline IRLS total score as a covariate by means of a shifted t-test and a 95% confidence interval. After non-inferiority was demonstrated we investigated superior efficacy of cabergoline compared to L-dopa.

Long-Term Treatment Period.

The primary efficacy criterion to evaluate superior efficacy of cabergoline over L-dopa was defined as the time to discontinuation from the study within 30 weeks due to a necessary change in RLS therapy because of augmentation or loss of efficacy of study treatments. Patients (ITT population) who completed the trial at Week 30 or patients who discontinued because of other reasons than augmentation or loss of efficacy were censored in the life-table analysis and evaluated according to the Kaplan-Meier statistic using Wilcoxon scores. Both primary endpoints were tested in a hierarchical order at a

TABLE 1. *Baseline characteristics of all treated patients*

Characteristic	Cabergoline (n = 178)	Levodopa (n = 183)
Age (yr)	56.9 ± 11.7	58.7 ± 11.6
Gender, no. (%)		
Male	58 (32.6)	46 (25.1)
Female	120 (67.4)	137 (74.9)
Race or ethnic group, no. (%)		
White	178 (100.0)	183 (100.0)
Start of first symptoms since (yr)	11.0 ± 12.0	12.1 ± 13.6
Course of disease since start of symptoms, no. (%)		
Continuous	61 (34.3)	60 (32.8)
Intermittent	16 (9.0)	18 (9.8)
Progressive	101 (56.7)	105 (57.4)
Need for drug therapy since (yr)	1.8 ± 2.3	1.9 ± 2.9
Patients with first-degree relatives with RLS, no. (%)	62 (34.8)	61 (33.3)
Augmentation/time shift during previous RLS treatment, no. (%)	35 (19.7)	35 (19.1)
IRLS total score	25.6 ± 7.2	25.8 ± 6.2

Plus–minus values are mean ± SD.
IRLS: International RLS Severity Scale.

one-sided type I error probability of a = 0.025, starting with the short-term criterion. The secondary efficacy variables were analyzed descriptively by tabulation of the parameters of the empirical distributions and by explorative 2-sample tests.

Based on the results from previous cabergoline studies,[19,20] 340 patients were estimated to be included into the trial to show non-inferior efficacy of cabergoline compared to L-dopa, 170 per treatment group (type I error: 0.025 (one-sided), type II error: 0.20, non-inferiorty margin: 3 points in the IRLS).

RESULTS

Subject Disposition and Demography

In total, 361 of 418 enrolled patients were treated in 51 centers, 178 in the cabergoline group, 183 in the L-dopa group. Baseline demographic and background characteristics are summarized in Table 1. Overall, treatment groups were comparable with respect to demographic and other baseline features.

Treatment

In the cabergoline group, 148 of 178 patients (83.1%) were treated with 2 mg and 30 patients (16.9%) with 3 mg/day. In the L-dopa group, 102 of 183 patients (55.7%) were treated with 200 mg/day whereas 81 patients (44.3%) needed a higher dose. More patients in the L-dopa than in the cabergoline group required a dose escalation after Week 6 ($P < 0.0001$, chi^2-test). The mean exposure time was 151 ± 81 days in the cabergoline group and 147 ± 78 days in the L-dopa group with no differences between the two treatment groups.

Efficacy Results

Primary.

Mean IRLS total scores were comparable in the two treatment arms at baseline (Table I). The baseline-adjusted LS mean point estimate for the difference in changes from baseline between the two groups was −6.6 points (95% Confidence Interval [−8.6 to −4.7]) in favor of cabergoline at the end of the short-term treatment period to L-dopa. Non-inferiority of cabergoline compared to L-dopa was confirmed, in addition, superior efficacy of cabergoline over L-dopa was demonstrated. (see confidence intervals in Table 2).

Regarding the time to discontinuation because of augmentation or loss of efficacy in the total 30-week treatment period, cabergoline showed superior efficacy to

TABLE 2. *Changes in the IRLS total score: during short- and long-term period*

Variable	Treatment	Unadjusted mean ± SD	LS-mean*	95% confidence interval	*P*-value
IRLS-difference	Cabergoline	−16.1 ± 10.2	−16.1	−17.5 to −14.7	<0.0001
Week 6/8–baseline	Levodopa	−9.6 ± 9.7	−9.5	−10.9 to −8.2	
Primary end point	Cab–Lev	n.a.	−6.6	−8.6 to −4.7	
IRLS-difference	Cabergoline	−15.6 ± 10.8	−15.7	−17.2 to −14.2	<.0001
Week 30–baseline	Levodopa	−8.8 ± 10.7	−8.7	−10.2 to −7.3	
Secondary end point	Cab–Lev	n.a	−7.0	−9.1 to −4.9	

P-values of the short-term measures are one-sided *P*-value for the shifted (by d = 3 IRLS points) hypothesis of noninferiority of cabergoline compared to L-Dopa.
*Calculated from an ANCOVA with factor treatment and covariate IRLS at baseline.
Cab, cabergoline; Lev, levodopa; SD, standard deviation; n.a, not applicable; Cab–Lev; difference between both treatments in changes from baseline.

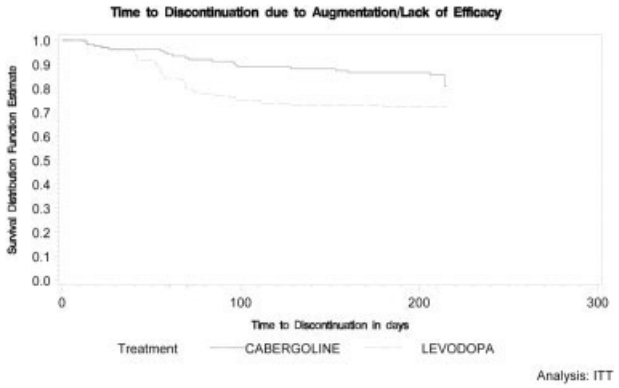

FIG. 2. Time to dropout due to augmentation/time shift or loss/lack of efficacy.

L-dopa (*P*-value for Wilcoxon score of life-table test: 0.0029, see Fig. 2, for rate of patients who discontinued due to either criterion or tolerated either event, see Table 3).

Secondary.

The difference between cabergoline and L-dopa in the IRLS total score remained fairly stable after the short-term period until study end (Table 2). In all scales which intend to measure changes in severity of RLS, improvements were larger in the cabergoline than in the L-dopa group (IRLS, RLS-6 scales, CGI). The analysis of the ASRS when it was at its maximum during the 30-week period showed lower total scores, on average, under cabergoline than under L-dopa (Table 4). A score of ≥ 1 in the 4 item version of the ASRS which cut-off might be suspicious for augmentation[16] was observed in 21.1% of the cabergoline and in 40.4% of the L-dopa group ($P = 0.0002$). More patients in the cabergoline (59.3%) than in the L-dopa group (29.4%) had a score of 10 or less in the IRLS total score at the end of the long-term period ($P < 0.001$).

TABLE 3. *Frequencies of augmentation/time shift or lack/loss of efficacy*

Variable	Cabergoline	Levodopa	*P*-Value
Discontinuation			
Both events	21 (11.9)	44 (24.0)	0.0029
Augmentation	7 (4.0)	18 (9.8)	0.0412
Loss of efficacy	14 (7.9)	26 (14.2)	0.0290
Discontinuation or tolerated			
Both events	34 (19.2)	71 (38.8)	0.0003
Augmentation	10 (5.6)	26 (14.2)	0.0104
Loss of efficacy	24 (13.6)	45 (24.6)	0.0100

The table reports absolute and relative frequencies of patients.

Discontinuation either due to augmentation/time shift or due to lack/loss of efficacy was the primary outcome measure, all other variables are secondary.

Values in parenthesis indicate percentage.

TABLE 4. *Further secondary efficacy variables (ITT)*

Variable	Baseline	End of period	*P*-value
RLS-6–severity at bedtime			
Levodopa	5.6 ± 2.9	−3.0 ± 3.7	0.0096
Cabergoline		−4.0 ± 3.2	
RLS-6–severity during the night			
Levodopa	6.5 ± 2.3	−3.6 ± 3.5	0.0001
Cabergoline	6.8 ± 2.3	−5.0 ± 3.2	
RLS-6–severity during the day/rest			
Levodopa	4.5 ± 2.6	−1.1 ± 3.7	<0.0001
Cabergoline	4.8 ± 2.7	−3.2 ± 2.9	
RLS-6–satisfaction with sleep			
Levodopa	6.7 ± 2.4	−2.7 ± 3.6	0.0241
Cabergoline	6.9 ± 2.5	−3.7 ± 3.6	
QoL–sum score			
Levodopa	41.4 ± 11.2	−10.6 ± 14.5	<0.0001
Cabergoline	42.0 ± 10.9	−17.7 ± 13.	
SF-A–quality of sleep			
Levodopa	2.3 ± 0.9	+1.0 ± 1.3	0.3401
Cabergoline	2.2 ± 0.9	+1.1 ± 1.2	
CGI–severity of illness			
Levodopa	4.6 ± 1.1	−1.3 ± 1.7	<0.0001
Cabergoline	4.6 ± 1.0	−2.2 ± 1.6	
ASRS–severity of augmentation			
Levodopa	0.63 ± 0.57	<0.0001	
Cabergoline	0.37 ± 0.48		

All analyses have been performed with the ITT analysis set.

Plus–minus values are means ± SD. Negative signs indicate improvements during treatment except for the SF-A where positive signs indicate improvement.

P-values associated with a Wilcoxon *U*-test for the comparison of different changes from baseline in the two groups for all secondary criteria.

Safety Results

Throughout the trial, day-time tiredness (ESS, RLS-6 scale) remained quite stable within groups and no remarkable difference was observed between the two treatment arms. According to the CGI "side effects" (investigator assessment) were better tolerated with L-dopa than with cabergoline (no or mild side effects: 95.5% in the L-dopa group, 85% in the cabergoline group, $P = 0.0056$), no difference was found in the patients' assessments. Seventy-four and 83 patients discontinued prematurely in the cabergoline group and in the L-dopa group during the 30-week treatment period (41.6% and 45.5%); discontinuations were equally distributed in the short- and the long-term period in both groups. Most patients discontinued the study because of adverse events, AEs (38 patients (21.3%) under cabergoline and 26 patients (14.2%) under L-dopa, for further details see Table 5).

TABLE 5. *Adverse Events*

Characteristic	Cabergoline (n = 178)	Levodopa (n = 183)
Patients with AEs	148 (83.1%)	142 (77.6%)
Number of AEs	501	326
Most frequent AEs[†]		
Nausea	55 (31.0%)	19 (10.4%)
Constipation	30 (16.9%)	5 (2.7%)
Headache	24 (13.5%)	17 (9.3%)
Fatigue	22 (12.4%)	8 (4.4%)
Somnolence	19 (10.7%)	7 (3.8%)
Abdominal pain upper	15 (8.4%)	5 (2.7%)
Vertigo	14 (7.9%)	7 (3.8%)
Diarrhea	12 (6.7%)	9 (4.9%)
Condition aggravated/augmentation	11 (6.2%)	32 (17.5%)
Dizziness	11 (6.2%)	5 (2.7%)
Nasopharyngitis	11 (6.2%)	8 (4.4%)
Hypertension	10 (5.6%)	4 (2.2%)
Hypotension	6 (3.4%)	1 (0.5%)
Hyperhidrosis	2 (1.1%)	7 (3.8%)
Patients with serious AEs	12 (6.7%)	9 (4.9%)
Number of serious AEs	16	11
Patients discontinued due to AEs[§]	47 (26.4%)	47 (25.7%)

Data are presented as absolute and relative frequencies of affected patients in the safety population. Relative frequencies are based on the sample size per treatment group.

[†]AEs which occurred in at least 5% of patients under either treatment are reported in the table.

[§]Condition aggravated or augmentations were also assessed as AE.

AE, Adverse event, all AEs which were reported by the investigators were analyzed.

In each group, three serious and treatment-related AEs therapy were documented in two patients. Under long-term treatment with cabergoline a 72-year-old male patient presented with cardiac arrhythmia and was admitted to hospital. A 53-year-old female patient experienced cardiac pain due to angina pectoris and dyspnoea, but no pathological findings were made upon admission to hospital. In both cases study drug was continued and patients recovered within several days. In the L-dopa group during the short-term period a 50-year-old male presented with depressive episodes and suicidal thoughts, and a 73-year-old woman experienced tachycardia. In both cases study drug was discontinued. No safety concerns are derived from these events when concomitant diseases were taken into account. No patient died in the course of the trial. For several adverse events, frequency was higher in the cabergoline than in the L-dopa group, and also domperidone was more frequently used in the cabergoline group (18% versus 7.1%, $P = 0.0030$). AEs occurred more frequently in the short-term than in the long-term period in the cabergoline group, no such differences were observed under L-dopa therapy.

DISCUSSION AND CONCLUSIONS

The CALDIR trial is the first large-scale study to compare head-to-head two active dopaminergic drugs in the treatment of RLS. In this 30-week study, superior efficacy could be demonstrated for cabergoline compared to L-dopa with improvement in total IRLS score and time to discontinuation because of augmentation or loss of efficacy in severely affected RLS patients. Superiority is further corroborated by several secondary outcome variables. These results are in line with previous studies[20-22] and classify cabergoline as one of the most effective treatments in RLS.

L-dopa, the active comparator to cabergoline, was efficacious in the treatment of RLS as measured by an average improvement of 8.7 points in the IRLS after 30 weeks. An improvement of comparable size was observed under placebo conditions of recently published placebo-controlled trials.[23-27] However, since this trial is the first head-to-head comparison of two active RLS treatments, nothing is known about the range of improvements of different drugs under the conditions of active-controlled trials without placebo control. In Europe, L-dopa is still a major treatment option for de novo RLS patients.

The design was developed for a fair comparison between both treatments. Although, one might argue that L-dopa was disadvantaged by a too low and not equivalent dose (200 to 300 mg) to 2 to 3 mg cabergoline, the dosages for both drugs in our study correspond to those which were effective in previous trials with cabergoline[20,21,28] and L-dopa.[29-31] They are used in clinical practice,[20] and equivalent dosages are applied in Parkinson's disease. Higher L-dopa dosages beyond 300 mg/day are associated with an increased risk for augmentation.[10] Moderate L-dopa dosages may also explain the augmentation rate of only 9.8% which is lower in this study than expected.[8,9] Retrospective data on augmentation show higher and less stable dosages compared to dosages in controlled trials.[9,32] L-dopa was given in two split doses to optimize the efficacy of this short-acting medication. This dosing regimen should meet as close as possible the pharmacological properties of both drugs and was derived from treatment practice in Parkinson's disease with a single cabergoline dosage and multiple L-dopa dosages.

This study reveals the difficulty to choose an appropriate matched dose for two medications in patients with RLS, as RLS adjusted equivalent doses are not available and therefore dosages known from PD have been used. Among those, the half-lives of both drugs are of most importance: cabergoline is expected to provide coverage for symptoms over 24 hours (half-life >65 hours)

whereas L-dopa is a short-acting compound (half-life 2 to 3 hours) and probably no more effective in the afternoon or early evening. When the study was planned in 2002, L-dopa plus benserazide was the only approved drug for RLS therapy in Germany and doses were selected according to the licensed use of L-dopa in RLS. Orientation on the doses used in clinical practice of comparator drugs when planning an active controlled trial probably contributes to more clinically valid information than other approaches that intend to compare pharmacologically equivalent dose regimens with the risk of a change in the benefit-risk-ratio to the disadvantage of the comparator.

In lack of standardized diagnostic methods, augmentation was assessed primarily by the investigators at each study site whose evaluations were based on clinical experience and training in the key features of augmentation prior to the study.[8] In addition, we used the ASRS which is a scale specifically designed to measure severity of augmentation.[16] Also in the ASRS total score, augmentation occurred on a low level for both groups, though more intensively under L-dopa than under cabergoline.

Compared to cabergoline, L-dopa was better tolerated and associated with fewer adverse events and more favorable tolerability ratings of the treating physicians. The rate of patients who were affected by AEs or who even discontinued due to AEs prematurely from the trial was fairly high and may be related to the predefined dose regimen, that did not allow to change doses flexibly after some weeks. The most frequent adverse events under cabergoline were gastrointestinal symptoms, headache, fatigue, and somnolence; except from headache those are well known side effects of cabergoline and other dopamine agonists. We did not monitor valvular fibrosis, as this was not reported as a major problem in ergot dopamine agonists at the time this study was planned. The incidence of both valvular fibrosis and other types of fibrosis still remains low during cabergoline therapy, but is a serious concern in treating PD patients. Its clinical relevance for RLS therapy has to be determined in future trials.[33]

In conclusion, both cabergoline and L-dopa were effective in treating RLS symptoms, whereas L-dopa was better tolerated, cabergoline was longer efficacious and showed less augmentation within 30weeks.

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APPENDIX

The following members of the CALDIR Study group participated in this study and contributed towards this report:

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